# DETERMINATION OF FIBRINOLYTIC ACTIVITY OF WHOLE BLOOD

## WITH SPECIAL REFERENCE TO THE EFFECTS OF EXERCISE AND FAT FEEDING

J. D. BILLIMORIA
M.Sc. Bombay, Ph.D. Lond.
LECTURER

JEAN DRYSDALE
B.Sc. Lond.
RESEARCH ASSISTANT

D. C. O. JAMES
M.B., B.Sc. Lond., B.Pharm. Wales
REGISTRAR

N. F. MACLAGAN
M.D., D.Sc. Lond., F.R.C.P.
PROFESSOR OF CHEMICAL PATHOLOGY

DEPARTMENT OF CHEMICAL PATHOLOGY, WESTMINSTER MEDICAL SCHOOL LONDON, S.W.1

SEVERAL writers have drawn attention to the possible importance of fibrinolytic processes in the ætiology of coronary atheroma (Duguid 1946, Morgan 1956).

Two more or less distinct fibrinolytic systems can be demonstrated in blood, one being relatively stable and requiring twelve to twenty-four hours for its action (Macfarlane 1937, Bidwell 1953, Fearnley and Tweed 1953, Greig 1956, Greig and Runde 1957, Buckell and Elliott 1959a and b), while the other is very labile but more rapidly active, requiring only one to eight hours for complete lysis. The labile system is subject to diurnal variation (Fearnley, Balmforth, and Fearnley 1957) and exhibits a definite arteriovenous difference (Fearnley and Ferguson 1957). These features imply a continuous production and destruction of this fibrinolysin, which may well be of more physiological significance than the stable one. Sherry, Fletcher, and Alkjaersig (1959) have suggested that this labile factor is a naturally occurring activator of plasminogen, possibly originating in the blood-vessels.

Methods employed for whole blood have been subject to certain technical difficulties. Thus fibrinolysis has so far been observed as an "all or nothing" phenomenon, the lysis-time being taken when the clot was seen to be totally disintegrated. In our experience, however, after partial lysis has occurred, it may be difficult to see small amounts of residual clot embedded in red cells, and this may lead to inaccurate recording of the end-point. Plasma-clot lysis takes up to twenty-four hours and in our hands yielded erratic and poorly duplicated results, partial lysis being difficult to observe.

The present paper reports a method which is rapid and reproducible and permits the quantitative assay of fibrinolytic activity of whole blood within a few hours. The method is concerned with the labile factor, and therefore the blood must be chilled immediately after collection. Several modifications of previous methods have been introduced, the most important being a colorimetric estimation of the hæmoglobin in the red cells trapped in the clot. The process of fibrinolysis is followed by observations on the loss of hæmoglobin from the disintegrating clot. To avoid measurements on residual traces of clot comparison of fibrinolytic activity of different blood specimens is made at the 50% level of clot lysis. With this procedure we have been able to study the effects of fat feeding, exercise, diurnal variation, and a number of minor but important factors which influence the fibrinolytic activity of whole blood.

### Materials

'AnalaR' reagents were used throughout the work except where otherwise stated.

*Phosphate buffer.*—23·9g.$Na_2HPO_4.12H_2O$ was dissolved in 1000 ml. of distilled water, and to this was added 3·02g.$KH_2PO_4$ dissolved in 250 ml. of distilled water. The final pH of the solution was 7·4. The buffer was heat-sterilised and stored at 4°C.

*Thrombin.*—Parke Davis topical thrombin (5000 National Institutes of Health units) was dissolved in 100 ml. sterile physiological saline at 0°C and stored in 3 ml. batches below −20°C. Thrombin solutions were stable for four weeks and were not used after this period.

*Glass cloth.*—'Tyglas' fabric quality no. Y83 (Fothergill & Harvey Ltd., Manchester, 2) was heated with concentrated $H_2SO_4$ containing a little $HNO_3$ to remove the plasticiser. The cloth was later washed free of acid, dried, cut into $1^1/_2$ in. squares, and moistened with cold saline before use.

*Glassware.*—Glass lysis tubes (100×12 mm.) were used; parafilm covers (GallenKamp Ltd., London, E.C.2) were cut into 1 in. squares and used as covers for the lysis tubes. All other glassware, syringes, and needles were siliconed before use. The glassware was siliconed with 'Repelcote' and the needles with M.S. 1107 siliconing fluid, using the methods recommended by the makers (Hopkin & Williams Ltd., Chadwell Heath, Essex).

*Colorimetric measurements.*—A 'Unicam' spectrophotometer S.P.600 was used. Lipæmia was measured in arbitrary units in 3 ml. tubes on a nephelometer (Evans Electroselenium Ltd., Harlow, Essex), using a turbidity standard supplied by the makers.

### Subjects and Method

The tests were carried out on 17 normal subjects and on 36 patients suffering from a variety of diseases including coronary occlusion, diabetes mellitus, cancer, myxœdema, &c. The number of patients, however, was too small to justify separate analysis, and the diagnoses are therefore not shown in the tables.

Blood was taken by a two-syringe technique using a siliconed 19-gauge needle and two siliconed syringes. Minimum stasis was applied during insertion of the needle only. Usually 9 ml. blood was withdrawn, and then the syringe was removed and a second one connected without moving the needle. 4·5 ml. of blood was drawn into the second syringe without stasis and added immediately to 95 ml. of ice-cold phosphate buffer containing 0·5 ml. of 3·8% (w/v) trisodium citrate in a siliconed 250 ml. stoppered flask. The blood was mixed by swirling in the ice-bath, and the flask was kept in crushed ice until used—usually within half an hour of drawing blood.

The thrombin solution (0·1 ml.) was placed in each of eighteen sterile glass lysis tubes. The diluted blood (4 ml.) was then added to each tube using a 25 ml. siliconed graduated wide-tipped pipette, and each tube was inverted once to ensure mixing, a parafilm cover being used for inversion. The tubes were allowed to stand for one minute, during which complete clotting occurred, and were then placed in crushed ice in a refrigerator for one hour. The concentration of the blood in the lysis tubes was 1/20 and the thrombin 1·25 units per ml.

The tubes were transferred to a 37°C water-bath and after ten minutes rolled vigorously between the palms to loosen the clots and allow retraction to occur, after which they were replaced in the bath for five minutes and then transferred to a 37°C incubator.

Thereafter at hourly intervals from placing the tubes in the 37°C bath, sets of three tubes were removed and placed in crushed ice to inhibit enzymatic activity. After a few minutes the clots were filtered on the prepared squares of glass cloth contained in a glass funnel, and immediately washed three times with 10 ml. of ice-cold saline to remove excess untrapped cells. The cloth and clot were then placed

in 7 ml. of 0·1N NaOH in a stoppered test-tube and shaken to aid dissolution of the clot. At this stage the mixture may be stored for several hours. The tubes were heated on a boiling water-bath for five minutes and cooled before reading the optical density at 540 mμ in a 1 cm. cell, this reading being taken as a measure of the alkaline hæmatin content. The mean readings for the three tubes was plotted against time, and the 50% lysis-time obtained as shown below.

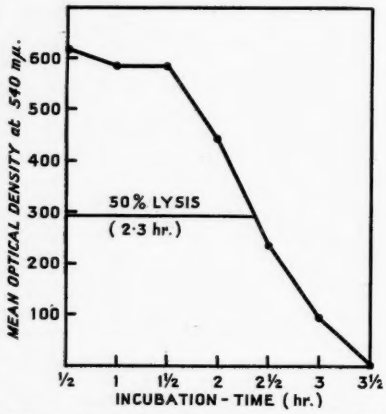



**Fig. 1—A typical determination of the 50% fibrinolysis-time of normal blood by alkaline hæmatin estimation.**

*Measurement of 50% Levels of Fibrinolysis*

Fig. 1 shows a typical experiment on the measurement of fibrinolysis. The hæmatin content of the blood-clot was initially read at half an hour after incubation at 37°C, and subsequently at half-hourly intervals; clot lysis did not occur for the first hour and a half, as seen from the plateau, but thereafter progressed rapidly. An hour after incubation, when the clot was fully retracted, its hæmatin reading was taken as a measure of the intact clot. The time taken for the reading to drop to half of this value was defined as the 50% fibrinolysis-time, which may be read from the graph. Further observations indicated that hourly determinations were adequate to give an accuracy to within ±0·1 hr.

## Initial Observations

A two-syringe technique of drawing blood was found to be essential since the first syringe usually gave more rapid lysis than the second (table I), presumably because of stasis.

TABLE I—EFFECT OF STASIS ON LYSIS-TIMES (HR.)

| Subject | Lysis-time 1st syringe (stasis) | Lysis-time 2nd syringe (no stasis) | Difference due to stasis |
|---|---|---|---|
| 1 | 2·7 | 3·3 | −0·6 |
| 2 | 3·9 | 4·3 | −0·4 |
| 3 | 2·5 | 2·8 | −0·3 |
| 4 | 1·6 | 1·6 | 0·0 |
| 5 | 2·3 | 2·4 | −0·1 |
| 6 | 4·2 | 4·3 | −0·1 |
| 7 | 3·4 | 5·2 | −1·8 |
| 8 | 1·8 | 2·3 | −0·5 |
| 9 | 2·7 | 3·0 | −0·3 |
| 10 | 3·4 | 3·8 | −0·4 |
| 11 | 2·7 | 3·0 | −0·3 |
| | | Mean | 0·44±0·15 |
| | | P<0·02 | |

*Storage of Blood*

We have confirmed the findings of Fearnley et al. (1957) that to preserve the thermolabile precursor of fibrinolysin it is essential to cool blood to 0°C rapidly after it is drawn. Blood drawn and immediately cooled and stored for varying periods does not readily lose its fibrinolytic property even after twenty-four hours. On the other hand, storage of blood for even half an hour at room temperature results in a total loss of fibrinolytic activity.

Once the blood was clotted, storage at 0°C or at room temperature did not result in rapid loss of fibrinolytic activity. Thus the specimens stored at 0°C for two hours remained almost unchanged. Those stored at room temperature, however, gave a slightly faster lysis-time, indicating that the fibrinolytic enzyme exerts a slow effect at room temperature; indeed storage at room temperature for twenty-four hours sometimes resulted in complete lysis before incubation.

*Effect of Thrombin and Citrate*

Previous work on thrombin concentration has shown that above 5 units per ml. thrombin was an inhibitor of fibrinolysis (Fearnley and Tweed 195′ In our experiments 2·5 units of thrombin per ml. were found to give the same lysis-times as 1·25 units. The latter was sufficient to give a firm clotting of a 1/20 diluted blood and was therefore adopted. Citrated or uncitrated blood specimens appeared to give the same fibrinolysis-times, and citrated blood was used in all subsequent experiments.

*Method of Dilution*

The method of diluting blood appeared to be particularly important. Thus, blood drawn in a syringe and transferred directly to the required volume of cold buffer-citrate mixture to give a 1/20 dilution ("predilution") gave shorter lysis-times than blood transferred from the syringe into a cold siliconed tube containing 1/10th volume of citrate and then diluted to 1/20 in the lysis tubes (table II).

TABLE II—EFFECT OF DILUTION AND STORAGE OF BLOOD ON LYSIS-TIMES (HR.)

| Blood specimen | Lysis-times | |
|---|---|---|
| | Prediluted | Undiluted |
| 1 | 2·4 | 2·6 |
| 2 | 3·3 | 4·0 |
| 3 | 3·4 | 3·9 |
| 4 | 3·7 | >6·0 |

Blood was stored for 1 hr. at 0°C in siliconed vessels with and without 1/20 dilution before clotting.

The bore of the pipettes used was also found to be important.

Table III shows that "prediluted" blood pipetted from a wide-bore pipette gave much faster lysis-times than the citrated whole blood diluted directly into lysis tubes as required. In the latter experiment a narrow-bore 0·2 ml. pipette was used for the dilution, but after this experiment the practice was avoided. Evidently surface effects created in such a pipette may be responsible for considerable inhibition of fibrinolysis.

*Dilution of Blood*

The fibrinolytic activity of blood increases with the degree of predilution of blood, and table IV shows a comparison of dilution ranging from 1/5 to 1/20. Dilutions of 1/5 and 1/7 gave erratic results and sometimes failed to demonstrate the natural fibrinolytic activity of blood.

TABLE III—EFFECT ON LYSIS TIME (HR.) OF PIPETTING WHOLE BLOOD THROUGH A NARROW PIPETTE

| Subject | Lysis-times | |
|---|---|---|
| | Narrow-bore pipette | Wide-bore pipette |
| 1 | No lysis | 3·2 |
| 2 | 5·0 | 2·6 |
| 3 | 3·9 | 2·5 |
| 4 | 4·3 | 3·3 |

TABLE IV—EFFECT OF VARIATION IN PREDILUTION OF BLOOD ON LYSIS-TIMES (HR.)

| Subject | Dilution of blood | | | |
|---|---|---|---|---|
| | 1/5 | 1/7 | 1/10 | 1/20 |
| 1 | .. | .. | 12·0 | 5·7 |
| 2 | .. | .. | 4·0 | 3·0 |
| 3 | .. | .. | 2·1 | 2·4 |
| 4 | .. | .. | 2·8 | 2·5 |
| 5 | .. | .. | 4·4 | 3·4 |
| 6 | .. | .. | 2·3 | 2·1 |
| 7 | .. | .. | 2·3 | 2·3 |
| 8 | 3·6 | 3·3 | .. | .. |
| 9 | 3·2 | 3·2 | .. | .. |
| 10 | 4·6 | 4·1 | .. | .. |
| 11 | >14·0 | >11·0 | .. | 2·5 |
| 12 | 24·0 | .. | .. | 2·5 |
| 13 | >24·0 | .. | .. | 3·5 |
| 14 | > 6·5 | .. | .. | 2·5 |
| 15 | >14·0 | .. | >14·0 | 3·7 |
| 16 | 3·4 | .. | 2·2 | 1·7 |

The 1/10 dilution appeared to be on the borderline and sometimes failed to show lysis, whereas the 1/20 dilution showed regular and rapid lysis. A 1/40 dilution of blood yielded fragile clots and the amount of red cells trapped in the clot appeared to vary from one tube to another. Hence all further experiments were conducted on a 1/20 dilution of blood. These observations led to the choice of the technique described above.

*Diurnal Variation*

It was essential for us to know whether diurnal variation of fibrinolytic activity (Fearnley et al. 1957) would affect our experiments, which were most conveniently carried out in the morning. Variations in fibrinolytic activity were therefore studied at 9.30 A.M. and 11.30 A.M. in 53 subjects after a fat-free breakfast taken at 7.30 A.M.

25 subjects who were confined to bed were grouped separately (rested group) from the other 28 who were allowed normal activity (active group) but were rested for half an hour before the test. Fibrinolysis-times for the active group were found to be significantly shorter at 11.30 A.M. than at 9.30 A.M. (table V), and the mean diurnal variation was $0{\cdot}82 \pm 0{\cdot}19$ hr., whereas no significant difference was observed in the rested group ($0{\cdot}28 \pm 0{\cdot}17$ hr.). Further analysis showed that the active group had lysis-times slightly longer at 9.30 A.M. and slightly shorter at 11.30 A.M. than the rested group. These differences, although not statistically significant, suggest that the effect of activity is exerted at both the times studied.

The experiments as a whole indicate that diurnal variation is at least partly dependent on physical activity. The extent of diurnal variation was such that experiments on individual subjects before and after fat feeding could not usefully be conducted on the same day.

*Day-to-day Variation*

In 4 subjects tested at the same time on different days there was comparatively little variation from one day to another (table VI). Thus for further work comparisons on fat-free and fatty meals were made at the same time on two different days.

*Normal Values*

The mean 50% lysis-times of 17 normal ambulant subjects after a fat-free breakfast were 3·18 hr. (S.D. 1·09) at 9.30 A.M. and 2·54 hr. (S.D. 0·63) at 11.30 A.M.

TABLE VI—DAY-TO-DAY VARIATION OF LYSIS-TIMES (HOURS) IN 4 SUBJECTS AFTER FAT-FREE BREAKFAST

| Subject | Day | Lysis-time at 10.00 A.M. | Lysis-time at 11.30 A.M. |
|---|---|---|---|
| A | 1 | 4·3 | 2·8 |
| | 2 | 3·9 | 3·2 |
| | 3 | 4·0 | 2·5 |
| B | 1 | 3·6 | 3·6 |
| | 2 | 3·5 | 3·6 |
| | 3 | 4·0 | 3·3 |
| C | 1 | 1·6 | .. |
| | 2 | 1·8 | .. |
| D | 1 | 3·0 | .. |
| | 2 | 3·0 | .. |
| | 3 | 3·4 | .. |

**Fat-feeding and Exercise Experiments**

Fibrinolysis measurements on 20 volunteers were made after fat-free and butter meals. The fat-free breakfast was given at 7.30 A.M. on one day and consisted of unlimited quantities of toast and jam and a cup of tea or coffee without milk. The fatty breakfast was given at the same time on another day and was essentially as above with the addition of $1\frac{1}{2}$ oz. (42 g.) butter. The results (table VII) show that with most subjects

TABLE V—DIURNAL VARIATION OF FIBRINOLYSIS-TIMES (HOURS)

| Subjects not confined to bed | | | | Subjects confined to bed | | | |
|---|---|---|---|---|---|---|---|
| Subject | Lysis-times (hr.) | | Diurnal variation | Subject | Lysis-times (hr.) | | Diurnal variation |
| | 9.30 A.M. | 11.30 A.M. | | | 9.30 A.M. | 11.30 A.M. | |
| 1 | 4·0 | 2·5 | +1·5 | 29 | 3·2 | 2·7 | +0·5 |
| 2 | 4·0 | 2·9 | +1·1 | 30 | 6·4 | 4·6 | +1·8 |
| 3 | 1·8 | 1·8 | 0 | 31 | 2·8 | 2·3 | +0·5 |
| 4 | 2·6 | 2·3 | +0·3 | 32 | 5·5 | 2·8 | +2·7 |
| 5 | 2·6 | 2·6 | 0 | 33 | 3·7 | 3·3 | +0·4 |
| 6 | 4·1 | 2·7 | +1·4 | 34 | 4·6 | 3·9 | +0·7 |
| 7 | 2·6 | 2·2 | +0·4 | 35 | 2·6 | 2·6 | 0 |
| 8 | 3·0 | 1·9 | +1·1 | 36 | 3·2 | 2·7 | +0·5 |
| 9 | 6·5 | 4·3 | +2·2 | 37 | 5·6 | 3·8 | +1·8 |
| 10 | 3·7 | 3·6 | +0·1 | 38 | 3·0 | 2·8 | +0·2 |
| 11 | 3·8 | 3·4 | +0·4 | 39 | 2·8 | 1·6 | +1·2 |
| 12 | 5·1 | 3·1 | +2·0 | 40 | 6·8 | 6·8 | 0 |
| 13 | 2·5 | 2·0 | +0·5 | 41 | 2·4 | 2·3 | +0·1 |
| 14 | 8·1 | 4·2 | +3·9 | 42 | 2·9 | 3·3 | −0·4 |
| 15 | 2·5 | 1·9 | +0·6 | 43 | 3·4 | 3·6 | −0·2 |
| 16 | 6·5 | 4·2 | +2·3 | 44 | 2·1 | 2·3 | −0·2 |
| 17 | 4·7 | 3·0 | +1·7 | 45 | 2·5 | 2·8 | −0·3 |
| 18 | 6·2 | 4·0 | +2·2 | 46 | 2·5 | 2·6 | −0·1 |
| 19 | 3·6 | 2·6 | +1·0 | 47 | 3·5 | 3·5 | 0 |
| 20 | 3·2 | 2·8 | +0·4 | 48 | 1·6 | 1·8 | −0·2 |
| 21 | 2·3 | 2·0 | +0·3 | 49 | 2·0 | 2·4 | −0·4 |
| 22 | 3·5 | 2·9 | +0·6 | 50 | 4·0 | 4·8 | −0·8 |
| 23 | 2·4 | 2·4 | 0 | 51 | 1·9 | 2·3 | −0·4 |
| 24 | 3·7 | 3·9 | −0·2 | 52 | 1·8 | 2·2 | −0·4 |
| 25 | 3·5 | 3·6 | −0·1 | 53 | 2·8 | 2·9 | −0·1 |
| 26 | 1·5 | 1·7 | −0·2 | | | | |
| 27 | 2·1 | 2·7 | −0·6 | | | | |
| 28 | 5·0 | 5·0 | 0 | | | | |
| Mean .. .. | 3·75 ± 0·28 | 2·93 ± 0·17 | +0·82 ± 0·19 P < 0·001 | Mean .. .. | 3·34 ± 0·28 | 3·06 ± 0·22 | +0·28 ± 0·17 not significant |

fibrinolysis-times were longer two hours after a fatty meal, the difference being significant at the 1% level (0·64±0·22 hr.). There was a rough but significant correlation between lipæmia and lysis-times (r=0·39) (fig. 2). At four hours after the meal there was no significant effect (0·34±0·23 hr.).

Experiments on the effect of exercise and fat feeding, alone and in combination, were carried out on 6 volunteers. The experiments were designed to test each subject on four separate days under the following conditions:

1. A fat-free breakfast with the subject at rest.
2. A fat-free breakfast, followed by a brisk walk of two miles in thirty minutes and then rest for one and a half hours.
3. A fatty breakfast at rest.
4. A fatty breakfast followed by a walk of two miles in thirty minutes and then rest for one and a half hours.

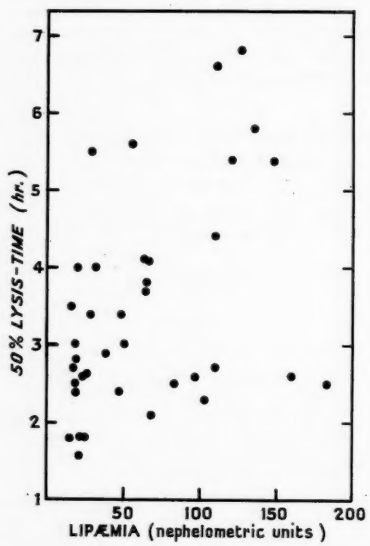



**Fig. 2—Correlation of 50% lysis-times with plasma turbidity in subjects with varying degrees of alimentary lipæmia. (r=0·39, P<0·02).**

In each case breakfast was taken at 8.00 A.M. and exercise, where applicable, was taken from 9.30 A.M. to 10.0 A.M. Blood samples were drawn at 10.00 A.M., 10.45 A.M., and 11.30 A.M.

The results of these experiments (table VIII) indicate that exercise has a considerable effect on accelerating the fibrinolytic activity. The mean difference in lysis-times at 10 A.M., immediately after exercise (columns B–D), was 1·66±0·28 hr. (P<0·01). This acceleration due to exercise is, however, transient and in 4 of the volunteers the lysis-times were restored to their original values after one and a half hours. Mean differences (B–D) at 10.45 A.M. and 11.30 A.M. were 0·63±0·02 (P<0·01) and 0·30±0·24 (not significant) respectively.

The inhibitory effect of fat (C–D), although statistically significant on the larger series of subjects reported above, was only observed in this experiment in 3 subjects at 10.00 A.M. Exercise after the fatty meal abolished the inhibiting action of fat on fibrinolysis in these 3 subjects. The mean difference due to exercise was thus little reduced by fat feeding (A–D), being 1·40±0·35 at 10 A.M. as compared with 1·66±0·28 without fat.

The combined effect of a fat-free meal with exercise compared with a fatty meal without exercise (C–B) showed the maximum difference in lysis-times at 10.00 A.M., viz., 1·96±0·50 (0·01<P<0·02). The plasma-turbidity measurements (table VIII) indicate that after a fatty meal exercise produced an earlier lipæmia,

TABLE VII—LYSIS-TIMES (HR.) TWO AND FOUR HOURS AFTER FAT-FREE AND FATTY MEALS (1½ OZ. BUTTER)

| Subject | Lysis-time at 9.30 A.M. | | Lysis-time at 11.30 A.M. | | Difference | |
|---|---|---|---|---|---|---|
| | No fat | Fat | No fat | Fat | Fat 9.30 A.M. | No fat 11.30 A.M. |
| 1 | 2·8 | 3·4 | 2·3 | 2·4 | +0·6 | +0·1 |
| 2 | 4·0 | 5·8 | 2·5 | 3·8 | +1·8 | +1·3 |
| 3 | 1·8 | 2·1 | .. | .. | +0·3 | .. |
| 4 | 4·0 | 5·4 | 2·9 | 3·4 | +1·4 | +0·5 |
| 5 | 1·8 | 2·9 | 1·8 | 2·5 | +1·1 | +0·7 |
| 6 | 1·8 | 2·5 | 2·2 | 2·8 | +0·7 | +0·6 |
| 7 | 1·5 | 2·3 | 1·7 | 2·6 | +0·8 | +0·9 |
| 8 | 2·8 | 3·7 | 2·5 | 3·7 | +0·9 | +1·2 |
| 9 | 2·4 | 3·7 | .. | .. | +1·3 | .. |
| 10 | 5·6 | 6·8 | 3·8 | 3·4 | +1·2 | −0·4 |
| 11 | 2·6 | 2·7 | 2·6 | 2·4 | +0·1 | −0·2 |
| 12 | 4·1 | 4·4 | .. | .. | +0·3 | .. |
| 13 | 3·8 | 6·6 | 3·4 | 4·3 | +2·8 | +0·9 |
| 14 | 3·4 | 5·4 | 4·2 | 4·0 | +2·0 | −0·2 |
| 15 | 2·5 | 2·4 | 2·0 | 1·8 | −0·1 | −0·2 |
| 16 | 3·5 | 2·6 | 3·7 | 1·6 | −0·9 | −2·1 |
| 17 | 5·5 | 4·1 | 2·8 | 4·3 | −1·4 | +1·5 |
| 18 | 2·7 | 2·5 | .. | .. | −0·2 | .. |
| 19 | 2·6 | 2·6 | 2·2 | 3·3 | 0·0 | +1·1 |
| 20 | 3·0 | 3·0 | .. | .. | 0·0 | .. |
| Mean .. .. .. .. .. .. | | | | | +0·64±0·22 P<0·01 | 0·34±0·23 |

TABLE VIII—EFFECT OF EXERCISE AND BUTTER MEALS ON FIBRINOLYSIS-TIMES AND LIPÆMIA

| Subject | Experiment | | | 50% lysis-times (hr.) | | | Lipæmia in nephelometric units | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Fat | Exercise | 10 A.M. | 10.45 A.M. | 11.30 A.M. | 10 A.M. | 10.45 A.M. | 11.30 A.M. |
| 1 | A | + | + | 2·4 | 2·4 | 2·4 | 24 | 15 | 14 |
| | B | − | + | 1·6 | 2·6 | 2·3 | 18 | 17 | 16 |
| | C | + | − | 3·4 | 2·5 | 2·4 | 48 | 32 | 20 |
| | D | − | − | 2·8 | .. | 2·3 | 17 | .. | 18 |
| 2 | A | + | + | 0·8 | 1·7 | 1·6 | 156 | 116 | 131 |
| | B | − | + | 0·8 | 2·0 | 1·3 | 18 | 16 | 14 |
| | C | + | − | 2·4 | 2·4 | 2·2 | 63 | 69 | 68 |
| | D | − | − | 2·4 | 2·7 | 2·5 | 17 | 15 | 17 |
| 3 | A | + | + | 2·6 | 3·2 | 3·4 | 178 | 161 | 86 |
| | B | − | + | 2·0 | .. | 2·7 | 33 | .. | 30 |
| | C | + | − | 5·8 | 5·2 | 3·8 | 134 | 94 | .. |
| | D | − | − | 4·0 | 3·6 | 2·5 | 31 | 28 | 25 |
| 4 | A | + | + | 1·6 | 2·6 | 2·7 | 161 | 102 | 53 |
| | B | − | + | 1·5 | 3·1 | 3·3 | 26 | 27 | 23 |
| | C | + | − | 4·1 | 4·1 | 3·6 | 112 | 143 | 118 |
| | D | − | − | 4·0 | 3·6 | 3·3 | 20 | 19 | 20 |
| 5 | A | + | + | 2·6 | 2·5 | 2·4 | 143 | 62 | 48 |
| | B | − | + | 2·4 | 2·5 | 1·8 | 20 | 23 | 20 |
| | C | + | − | 2·5 | 2·3 | 2·5 | 82 | 62 | 50 |
| | D | − | − | 3·0 | .. | 2·7 | 31 | .. | 29 |
| 6 | A | + | + | 1·5 | 2·8 | 2·4 | 38 | 24 | 29 |
| | B | − | + | 1·6 | 2·4 | 2·7 | 15 | 16 | 18 |
| | C | + | − | 3·5 | 3·1 | 3·1 | 58 | 40 | 29 |
| | D | − | − | 3·7 | 3·1 | 2·6 | 13 | 13 | 14 |

possibly due to accelerated absorption of fat. The intensity of lipæmia showed no consistent alteration.

*Stypven Clotting-times*

During this study observations of the Stypven clotting-time by the method of Maclagan, Billimoria, and Curtis (1958) were also made. These showed the expected shortening of clotting-times after the butter feeds, but exercise produced no appreciable effect.

## Discussion

The present work was undertaken as part of an investigation of the possible role of fibrinolysis in the ætiology of atheroma. Preliminary experiments indicated the need of a more accurate method for determining the labile fibrinolytic activity of blood, and for a study of the effect of various factors on this activity. The method presented employs whole blood and gives fairly rapid lysis-times of 2–4 hours, reproducible to $\pm 0{\cdot}1$ hours. The end-point is read at a 50% level of lysis, the degree of lysis being measured by hæmoglobin estimations.

Incidentally, if the terminology recently suggested by Sherry et al. (1959) be accepted, the method should be described as one for "thrombolysis" rather than for "fibrinolysis", the latter term being reserved for techniques employing purified fibrin.

A number of apparently minor technical points were found of great importance. Thus a two-syringe technique was necessary and stasis had to be avoided since it produced a faster lysis-time. This observation is in agreement with the arteriovenous difference reported by Fearnley et al. (1957), who found that venous blood lysed more rapidly than arterial blood. Immediate predilution of the blood after collection was also found to be essential.

We confirmed the finding of Greig and Runde (1957) and of Nitzberg et al. (1959) that butter feeding produces significant inhibition of lysis, but were also able to separate this effect from that due to diurnal variation. Our experiments differed from many other fat-feeding experiments in that smaller amounts of fat were administered ($1^1/_2$ oz.). While lipæmia produced in this way does not last as long as that produced by larger feeds, we felt that the conditions were more physiological. In these experiments there was a significant correlation between inhibition and the degree of visible lipæmia; but this correlation was only a rough one, suggesting that some lipid other than that present in chylomicra is responsible for the inhibition.

The effects of exercise were of interest firstly because of previous work demonstrating stimulation of fibrinolysis by exercise (Biggs, Macfarlane, and Pilling 1947) and secondly because of suggestions that lack of exercise may be an ætiological factor in coronary disease (Morris, Heady, Raffle, Roberts, and Parks 1953, McDonald and Fullerton 1958). As expected, moderate exercise produced a considerable acceleration of lysis which was sufficient to overcome the effects of fatty meals. The combined effects of inactivity and fat feeding were particularly impressive, producing about double the active control lysis-times. These findings obviously indicate the need for careful control of diet and activity in work of this kind, and probably patients in whom fibrinolytic activity is to be tested should be prepared almost as carefully as for an estimation of basal metabolic rate.

It would obviously be premature to claim any connection between these results and the ætiology of atheroma. If there is indeed any connection between atheroma and deficient fibrinolysis, our results would be consistent with current speculations on the effects of dietary fat in promoting, and of exercise in limiting, the development of atheroma. Further work on patients with coronary disease is in progress which we hope may throw further light on this problem.

## Summary

1. A new method of determining the fibrinolytic (thrombolytic) activity of whole blood is described in which the rate of lysis is followed by means of hourly estimations of the hæmoglobin content of the clot. A graph may then be plotted and the time for 50% lysis determined.

2. Venous blood was found to be satisfactory if collected without stasis, which produces a significant shortening of the lysis-time ($0{\cdot}44 \pm 0{\cdot}15$ hr.).

3. Existence of a diurnal variation in lysis-times was confirmed by a study on 53 subjects tested after a fat-free meal. This diurnal variation was significant only in subjects not confined to bed ($0{\cdot}82 \pm 0{\cdot}19$ hr.). Normal lysis-times for 17 ambulant subjects after a fat-free breakfast were $3{\cdot}18 \pm 0{\cdot}27$ hr. at 9.30 A.M., and $2{\cdot}54 \pm 0{\cdot}15$ hr. at 11.30 A.M.

4. The effects of butter feeding on 20 volunteers showed a significant inhibition of lysis-times two hours after the meal ($0{\cdot}64 \pm 0{\cdot}22$ hr.). There was a significant general correlation between lipæmia (plasma turbidity) and inhibition of lysis ($r = 0{\cdot}39$, $P < 0{\cdot}02$).

5. In 6 normal subjects moderate exercise accelerated fibrinolysis considerably ($1{\cdot}66 \pm 0{\cdot}28$ hr.). The effect was transient and had usually disappeared after one and a half hours, but exercise was capable of overcoming the inhibitory effect of butter feeding. Lipæmia was not diminished but after exercise it tended to occur sooner. Exercise produced no significant change in the 'Stypven' clotting-times.

This work was supported by generous grants from the endowment funds of Westminster Hospital. We are also much indebted to the medical and surgical staff of Westminster Hospital for access to patients; to the normal subjects who cooperated in the tests; to Miss Sheila Pateman for technical assistance; and to Dr. J. G. Humble for helpful discussion.

## REFERENCES

Bidwell, E. (1953) *Biochem. J.* **55**, 497.
Biggs, R., Macfarlane, R. G., Pilling, J. (1947) *Lancet*, i, 402.
Buckell, M., Elliott, F. A. (1959a) *ibid.* i, 660.
— — (1959b) *ibid.* p. 662.
Duguid, J. B. (1946) *J. Path. Bact.* **58**, 207.
Fearnley, G. R., Balmforth, G., Fearnley, E. (1957) *Clin. Sci.* **16**, 645.
— Ferguson, J. (1957) *Lancet*, ii, 1040.
— Tweed, J. M. (1953) *Clin. Sci.* **12**, 81.
Greig, H. B. W. (1956) *Lancet*, ii, 16.
— Runde, I. A. (1957) *ibid.* ii, 461.
Macfarlane, R. G. (1937) *ibid.* i, 10.
Maclagan, N. F., Billimoria, J. D., Curtis, C. (1958) *ibid.* ii, 865.
McDonald, G. A., Fullerton, H. W. (1958) *ibid.* p. 600.
Morgan, A. D. (1956) The Pathogenesis of Coronary Occlusion. Oxford.
Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G., Parks, J. W. (1953) *Lancet*, ii, 1053, 1111.
Nitzberg, S., Peyman, M., Goldstein, R., Proger, S. (1959) *Circulation*, **19**, 676.
Sherry, S., Fletcher, A. P., Alkjaersig, N. (1959) *Physiol. Rev.* **39**, 343.

". . . Every investigator, in the natural as well as in the social sciences, has a certain predisposition to fall in love with his own hypotheses and to cling to them fondly. No one likes to be proved wrong. But the experience is exceptionally distressing when the beloved hypothesis was chosen for its moral as much as for its intellectual qualities—as is the case, for example, with theories that postulate that delinquency is due to the decay of religious observance, or to mothers going out to work, or to broken homes, or to failure to take advantage of youth clubs. . . . Such theories are put forward by people who want them to be true. They are derived from the moral systems of those who propound them, and not from study of the relevant facts."—Baroness WOOTTON OF ABINGER, *Listener*, Sept. 17, 1959, p. 437.

# RECIPROCAL SKIN GRAFTS IN A PAIR OF TWINS SHOWING BLOOD CHIMÆRISM

M. F. A. WOODRUFF
M.D., M.S. Melb., F.R.C.S.
PROFESSOR, DEPARTMENT OF SURGICAL SCIENCE, UNIVERSITY OF EDINBURGH

BERNARD LENNOX
M.D. Durh., Ph.D. Lond., M.R.C.P., F.R.F.P.S.
SENIOR LECTURER, DEPARTMENT OF PATHOLOGY, UNIVERSITY OF GLASGOW

Owen (1945) demonstrated that the blood of newborn non-identical cattle twins usually contains erythrocytes of two distinct serological types. He attributed this to exchange of blood during intrauterine life, since cattle twins are commonly synchorial. It was later shown that this state of "blood chimærism" persists for much longer than the life of the erythrocyte; it follows, therefore, that erythropoietic cells must have been exchanged and have continued subsequently to produce erythrocytes of characteristic serological type (see Owen et al. 1946, Stone et al. 1952).

Blood chimærism is but one manifestation of immunological tolerance of homologous tissue. This became apparent when Medawar and his colleagues (Anderson et al. 1951, Billingham et al. 1952) showed that skin homografts exchanged between dizygotic cattle twins survived usually for long periods, and sometimes permanently, without regard to differences of sex or colour; on the other hand, similar homografts exchanged between calves other than twins (including siblings of independent birth) were rapidly destroyed. It was therefore a reasonable prediction (Woodruff 1953), when the first report of a human blood chimæra was published by Dunsford et al. (1953), that this individual would be tolerant of skin homografts from her twin. Unfortunately the twin was no longer alive, and an opportunity of investigating the matter did not arise until another pair of human chimæras was discovered by Booth et al. (1957). The following is an account of our findings in this second pair.

## Investigation

The twins were 21 years old and were of opposite sex. Booth et al. (1957) had found that the blood of each contained red cells of group A and group O in the following proportions:

| | A | O |
|---|---|---|
| Male twin .. .. | 86% | 14% |
| Female twin .. .. | 1% | 99% |

In addition, the blood of the male twin had been found to contain a proportion of polymorphonuclear leucocytes showing female sex chromatin.

The twins generously agreed to submit to reciprocal skin grafting and this was performed by one of us (M. F. A. W.) in November, 1957. A full-thickness graft about 1 cm. square was removed from the volar aspect of the wrist of each twin under local (xylocaine) anæsthesia, and sutured in place in the corresponding defect on the other twin. The site for the grafts was determined mainly by the wishes of the twins themselves. The grafts were measured carefully at the conclusion of the operation, and were examined and measured again 1, 2, and 4 weeks after grafting, and then at monthly intervals. After a year a biopsy specimen was taken, samples of blood were obtained for further grouping, and smears of buccal mucosa (Moore and Barr 1955) for chromatin sexing.

## Results

*Macroscopic Appearance of the Skin Grafts*

The grafts measured initially 1·3 × 1·0 cm. and 1·4 × 1·1 cm. on the male and female twins respectively. Both healed in well, did not vary in size by more than 0·1 cm. in either dimension during the whole period of observation, and never showed any trace of scabbing.

The graft on the male twin behaved macroscopically just like an autograft. 2 weeks after grafting it was supple and only slightly deeper in colour than the surrounding skin. Later it became indistinguishable in colour from host skin, but throughout the period of observation it retained the finer pattern of surface ridges and grooves characteristic of female skin (fig. 1).

For 6 months the graft on the female twin appeared decidedly deeper in colour than the surrounding host skin. Thereafter when the hands were warm there was little difference in colour between graft and host skin, but when the hands were cold the graft was somewhat more cyanotic. The graft retained the coarse pattern of surface markings characteristic of male skin (fig. 1).

*Histological Findings*

The biopsy specimens were fixed in modified Davidson's fixative for 24 hours, followed by saturated $HgCl_2$ in formalin for 3 hours. They were then double-embedded in celloidin and paraffin by a rapid method developed by Russell (1956). Sections cut at 12 $\mu$ and stained by Feulgen's method were found most useful for sexing nuclei, these relatively thick sections being especially helpful with the large and often irregular nuclei of the dermal fibroblasts. Excellent preparations were obtained from each twin.

*Male twin.*—The specimen after fixation was about 15 mm. long. It consisted of healthy skin with normal epidermis, dermis, and sweat glands, but no hair follicles. The epidermis appeared quite uniform from end to end of the specimen: the dermis was rather frayed at the ends, so that the exact site of junction of graft and host tissues

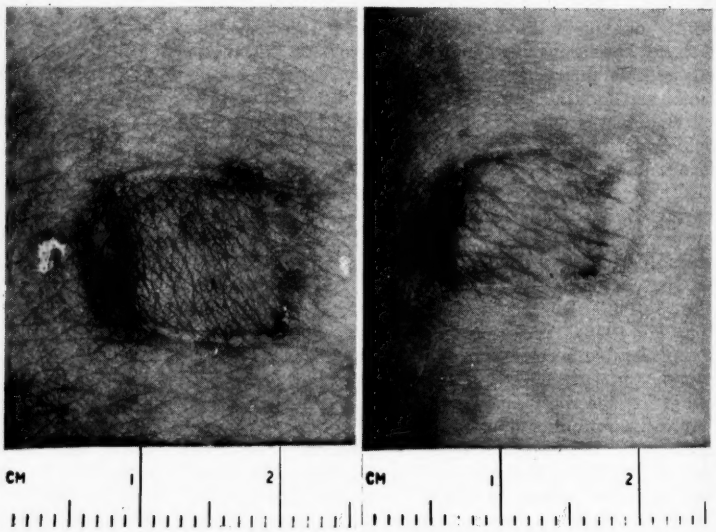



**Fig. 1—Gross appearance of the grafts when they had been in place for six months.**
The graft on the male twin, reproduced on the left, shows the fine surface markings characteristic of female skin against a background of coarsely patterned male type skin. The graft on the female twin is reproduced on the right, and here the graft shows the coarse pattern of male skin, while the surrounding skin is finely patterned.

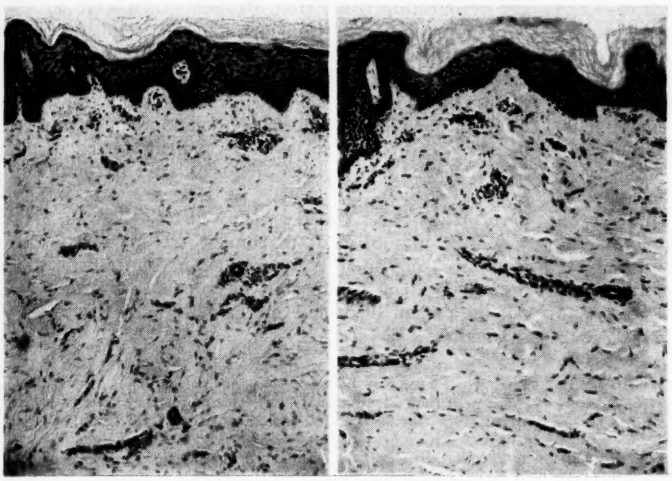


**Fig. 2—Sections from central portion of each graft.**

The graft on the male twin is shown on the left; except for hyperkeratosis and a mild perivascular infiltrate, it has the appearance of normal skin. By nuclear sexing all the tissue shown is male. The graft on the female twin, shown on the right, is similar in general structure. By nuclear sexing all the tissue shown is male. (Hæmatoxylin and eosin × 60.)

could not be identified, but there was certainly no conspicuous line of demarcation. The only obvious deviation of the whole from normal skin was a sprinkling of perivascular dermal infiltration, of the familiar lymphocyte-histiocyte type seen in so many non-specific skin conditions, at intervals throughout the specimen and at all depths (fig. 2).

On nuclear sexing the whole epidermis and the sweat-glands were quite unmistakably male, and the quality of the nuclear detail in the epidermis at least was such that we can rule out the possibility that technical defects resulted in failure to demonstrate the sex chromatin. Among the dermal fibroblasts the position was somewhat different. Over most of the area they were unmistakably male, the percentage with anything remotely resembling sex chromatin never rising above 2·5. In one small area, seen in only two sections and not above 1 mm. in diameter in any direction, there seemed to be an undue proportion of nuclei containing sex chromatin. Within this area two separate groups of fifty adjacent nuclei were found among which twenty-nine and nineteen contained sex-chromatin bodies. Because of the small number of nuclei involved one cannot altogether rule out the effects of chance and bias in making these counts, but it seems likely that these represent islands of surviving female cells in a predominantly male tissue. Apart from the presence of sex chromatin, the cells concerned did not appear in any way remarkable, and there was no increase of cellular infiltration in the neighbourhood: the area concerned could not in fact be distinguished from the surrounding tissues without using the oil-immersion lens.

*Female twin.*—The specimen after fixation was about 14 mm. long and in general structure exactly like the other. The epidermis and sweat-glands appeared normal, there was no definite line of demarcation between graft and host, and there was non-specific perivascular infiltration of similar degree to that seen in the other specimen (fig. 2).

By nuclear sexing, however, the tissue at each end of the biopsy was clearly female, while that in the centre was male. This applied to both epidermis and dermis, though male nuclei extended a little further out in the dermis than in the epidermis. The central band of male epidermis, measured at several levels through the block of tissue, was 8–9 mm. wide. At one side a good deal of mixing of cells seemed to have occurred, patches of male and female nuclei being intermingled over a distance of about a millimetre: on the other side the transition was more abrupt.

*Blood-grouping*

Blood-grouping was repeated at the time of the graft biopsy to determine whether the twins were still chimæras.

This was kindly undertaken by Dr. P. L. Mollison, director of the Blood Transfusion Research Unit of the Medical Research Council, who reported that by differential agglutination 17% of the red cells of the male twin were estimated to be group O, and about 2% of the sister's cells were group A. The figure of 17% was based on counting; the figure of 2% was based on comparisons with known mixtures. As a further check Dr. Mollison labelled the sister's blood with $^{51}Cr$, and then lysed the A cells with potent anti-A immune serum and measured the amount of $^{51}Cr$ liberated. He concluded that the blood contained more than 1% of $A_1$ cells but less than 3%.

It is clear therefore that the twins are still chimæras, and that the proportion of foreign cells in the blood shows no decrease * after the interchange of skin grafts.

*Buccal Mucosal Smears*

Buccal mucosal smears confirmed that the cells of the female twin were cytologically female in type whereas those of the male twin were cytologically male.

## Discussion

The findings suggest that the female twin is completely tolerant of her brother's skin. To put the matter beyond all possible doubt it might be desirable to study the behaviour of a second-set graft (cf. Woodruff and Simpson 1955), but we have not thought it justifiable to impose this additional burden on our very willing subjects. The difference in colour between the graft and the host skin, which was observed to persist for several months, was at first thought to indicate a homograft reaction; but similar differences may occur with autografts and the subsequent history and histological findings would suggest that the observation was not of immunological significance.

Had nuclear sexing not been undertaken it would have seemed reasonable to conclude that the male twin similarly was completely tolerant of his sister's skin, but the results of this investigation suggest that nearly all the cells of the graft had been replaced by cells of host origin. With a few exceptions, unimportant in the present context, tissues from women are characterised by the presence of the sex chromatin in most nuclei, while tissues from men are equally well characterised by its absence or rarity (Moore and Barr 1954, Lennox 1956). This difference endures from the early embryo to death, and is not modified by pathological changes occurring in the tissues, though it may be obscured by gross alterations in nuclear morphology.

* There appears in fact to have been a slight increase, but not of sufficient magnitude to be significant.

The fact that the cells of a graft are replaced does not necessarily imply that the graft is immunologically unacceptable, for massive orthotopic bone grafts appear to be systematically replaced even when they are autologous. Little is known of the extent to which replacement occurs in skin autografts and it is difficult to design experiments which will throw light on the matter; but it is conceivable that the replacement which was observed in the present investigation could occur in an autograft in the course of a year, and if this were true the findings would not be incompatible with the existence of complete immunological tolerance. This explanation is open to the objection that replacement occurred in only one of the grafts —an objection which, if not decisive, is at any rate formidable.

The alternative hypothesis is that the male twin was only partially tolerant of his sister's tissues, but here again difficulties arise. There is some cellular reaction in both grafts, which might be regarded as evidence of an immune reaction; but it is so slight that, in view of our lack of knowledge of the histology of free autografts of this age in man, we are reluctant to attach any special significance to it. Secondly, the male twin showed in his blood a much higher proportion of foreign cells than his sister, and might therefore be expected to show at least as high a degree of tolerance, assuming that the interchange of hæmopoietic cells took place in both directions at the same time. This assumption may not be correct, but it appears reasonable. Finally, in neither twin was there any change in the proportions of A and O erythrocytes, which seems to imply either that tolerance was complete, or alternatively that some form of adaptation (Woodruff 1959) had occurred in the marrow transferred from the female to the male twin during intrauterine life.

It seems clear that further evidence is required to determine which explanation is correct, but this is not easy to obtain.

Unfortunately the species in which blood chimærism among dizygotic twins is quite common (i.e., the cow) is unsuitable for nuclear sexing. In man, on the other hand, nuclear sexing is easy, and has already been used as a criterion of survival of homografts of skin and cartilage by Peer (1957, 1958), but blood chimærism appears to be extremely rare. In the rabbit (Davidson et al. 1958, Porter and Murray 1958) and dog (Porter and Couch 1959) polymorph sexing has been used to establish the survival of marrow homografts, but so far as we know no other tissues have been successfully identified in this way. Sexing of skin is feasible in monkeys (Prince et al. 1955) and cats (Graham and Barr 1952), and if tolerance to homologous tissues could be induced in these species the way would be open for experimental investigations of the problem; failing this further elucidation must await the discovery of additional human chimæras.

The fact that one twin at least appeared to be completely tolerant is of special interest in view of the fact that it has not so far proved possible to induce tolerance to homologous tissue in man. Attempts to do this (Woodruff 1957) in infants at birth met with very limited success, and had to be abandoned when the phenomenon of runt disease was discovered in experimental animals. The twins in the present investigation, like cattle twin chimæras, did not show any evidence of ill-effects due to a graft-against-host reaction, presumably because any immunologically competent cells in the tissue which was exchanged during intrauterine life were themselves immature. This suggests that in man, as in animals (see Barnes et al. 1956, Congdon and Urso 1957), tolerance to homografts could be induced artificially without danger by injecting tissue from fœtuses which were sufficiently immature, and by analogy fœtal hæmopoietic tissue should not cause secondary disease when injected into heavily irradiated patients. In fact the risk of secondary disease in man after total body irradiation and transplantation of homologous adult hæmopoietic tissue cannot yet be assessed, because so far every patient treated in this way appears either to have died soon after irradiation or to have rejected the grafts. At least one attempt has nevertheless been made (McWhirter, Newall, and Woodruff unpublished) to combat the marrow aplasia resulting from total body irradiation by transplanting exclusively fœtal homologous hæmopoietic tissue (liver), but the patient died of severe hæmorrhage 17 days after irradiation.

We are deeply grateful to the twins for their ready cooperation and for their interest in the whole investigation. It is a pleasure to record that they have recently been selected for the Oliver memorial award, 1958, for service in the field of blood-transfusion. We are indebted also to Dr. J. D. James and Dr. R. R. Race for their helpful cooperation, to Dr. P. L. Mollison for the blood investigations, and to Dr. P. N. Cardew, head of the department of photography at St. Mary's Hospital, for photographing the grafts and for providing fig. 1. Part of the cost of the investigations has been met from the Wilkie Fund for Surgical Research (University of Edinburgh).

REFERENCES

Anderson, D., Billingham, R. E., Lampkin, G. H., Medawar, P. B. (1951) *Heredity*, **5**, 379.
Barnes, D. W. M., Corp, M. J., Loutit, J. F., Neal, F. E. (1956) *Brit. med. J.* ii, 626.
Billingham, R. E., Lampkin, G. H., Medawar, P. B., Williams, H. L. (1952) *Heredity*, **6**, 201.
Booth, P. B., Plaut, G., James, J. D., Ikin, E. W., Moores, P., Sanger, R., Race, R. R. (1957) *Brit. med. J.* i, 1456.
Congdon, C. G., Urso, I.S. (1957) *Amer. J. Path.* **33**, 749.
Davidson, W. M., Fowler, J. F., Smith, D. R. (1958) *Brit. J. Hæmat*, **4**, 231.
Dunsford, I., Bowley, C. C., Hutchison, A. M., Thompson, J. S. (1953) *Brit. med. J.* ii, 81.
Graham, M. A., Barr, M. L. (1952) *Anat. Rec.* **112**, 709.
Lennox, B. (1956) *Scot. med. J.* i, 97.
Moore, K. L., Barr, M. L. (1954) *Acta anat.* **21**, 197.
— — (1955) *Lancet*, ii, 57.
Owen, R. D. (1945) *Science*, **102**, 400.
— Davis, H. P., Morgan, R. F. (1946) *J. Hered.* **37**, 290.
Peer, L. A. (1957) *Transpl. Bull.* **4**, 109.
— (1958) *ibid.* **5**, 404.
Porter, K. A., Couch, N. P. (1955) *Brit. J. exp. Path.* **40**, 52.
— Murray, J. E. (1958) *J. nat. Cancer Inst.*, **20**, 189.
Prince, R. H., Graham, M. A., Barr, M. L. (1955) *Anat. Rec.* **122**, 153.
Russell, N. L. (1956) *J. med. Lab. Technol.* **13**, 484.
Stone, W., Stormont, C., Irwin, M. R. (1952) *J. Anim. Sci.* **11**, 744.
Woodruff, M. F. A. (1953) *Brit. med. J.* ii, 1103.
— (1957) *Transpl. Bull.* **4**, 15.
— (1958) *Klin. Wschr.* **36**, 245.
— (1959) International Colloquium on Biological Problems of Grafting. Liège.
— Simpson, L. O. (1955) *Brit. J. exp. Path.* **36**, 494.

# RETINOPATHY FOLLOWING CHLOROQUINE THERAPY

H. E. HOBBS
M.B. Lond., F.R.C.S.
OPHTHALMIC SURGEON, ROYAL FREE HOSPITAL, LONDON, W.C.1, AND MAIDA VALE HOSPITAL FOR NERVOUS DISEASES

A. SORSBY
M.D. Leeds, F.R.C.S.
RESEARCH PROFESSOR IN OPHTHALMOLOGY, ROYAL COLLEGE OF SURGEONS, LONDON, W.C.1

A. FREEDMAN
M.D. Lond., M.R.C.P.
ASSISTANT PHYSICIAN, HACKNEY HOSPITAL, LONDON, E.8

SYNTHETIC antimalarial drugs have become valuable therapeutic agents in certain chronic diseases since Page (1951) noted the beneficial effect of mepacrine in lupus erythematosus. Mepacrine was found useful also in rheumatoid arthritis (Freedman and Bach 1952). Long-continued use of mepacrine, however, discolours the skin and has been known to cause aplastic anæmia. Moreover, Dame (1946) found evidence that retinal changes and

defects of the central visual fields were related to high blood-mepacrine levels. Accordingly some other antimalarial drugs have latterly been preferred, among which the chloroquine compounds, since they were first developed, have had the longest trial.

In the doses used to suppress or treat malaria, the toxic effects of chloroquine and its derivatives are only minor and have not impaired their usefulness. In higher dosage, on the other hand, more serious side-effects have been known since the earliest trials with chloroquine (Alving et al. 1948). Since in both lupus erythematosus and rheumatoid arthritis the effective dose commonly exceeds that used for malaria, and the drug is administered for much longer periods, it is not surprising that toxic effects have been reported. Among these, ill-defined subjective disturbances of vision were observed early (Alving et al. 1948, and many others). A more specific and lasting disturbance, produced by corneal deposits, was noted (Hobbs and Calnan 1958) in patients with lupus erythematosus treated with chloroquine sulphate. Its existence has been confirmed in a number of clinics, and further reported upon by Zeller and Deering (1958) and by Leopold (1958), although it was not seen by Bagnall (1957). Similar changes have also been seen after treatment with hydroxychloroquine sulphate, and amodiaquine hydrochloride (Marx 1959). The corneal deposits are not yet known to cause serious permanent visual defect (Hobbs and Calnan 1958, Leopold 1958).

Recently we have seen changes of a much graver character, with visual damage which, in some cases at least, is evidently irreversible. These patients, too, were under treatment with chloroquine compounds for lupus erythematosus and rheumatoid arthritis.

### Case-reports

**Case 1.**—A clerk, aged 58, had had discoid lupus erythematosus for some twenty-three years, and had been treated with chloroquine in doses of 100–600 mg. per day from June, 1954, to November, 1957. Treatment was then withdrawn because he said that, in the space of a few weeks, he had become " almost blind " in the dark, and had had difficulty in reading: he seemed to see " only half an object " and " words tended to disappear ". For the next few months, therefore, he was given hydroxychloroquine sulphate instead of chloroquine.

On ocular examination on Dec. 5, 1958 (H. E. H. and A. S.), the patient said that his condition was unaltered since its appearance. We found the corrected visual acuity was slightly impaired (6/9; 6/6). The peripheral visual fields showed severe loss on the temporal sides, affecting principally the upper quadrant on the left, and also involving most of the lower quadrant on the right side. Additional paracentral scotomata were plotted in the central fields. Both optic fundi showed rather pale discs with narrowing of the vessels in all areas of the retina. In the periphery there was an irregular mottled pigmentation in both fundi; and at both maculæ there was an aggregation of fine pigment, greater on the right side than on the left, where it formed a small ring surrounding the fovea. The pigmented line in the corneal epithelium, seen in other cases treated with chloroquine, was just apparent, and occasional snowflake opacities could be seen in the anterior cortex of the lenses.

**Case 2.**—A woman of 60 had suffered from rheumatoid arthritis for about thirty years and had been under the care of one of us (A. F.) for six years. She had begun treatment with mepacrine (100 mg. b.i.d.) five years previously and had benefited considerably. A year later chloroquine was substituted (200–300 mg. per day) and on this she had continued for almost three years, until she complained of misty vision and inability to see the whole of words when reading. Ophthalmoscopy at that time revealed that the arteries were narrowed and the maculæ abnormal, and chloroquine was discontinued, prednisolone being substituted for it. Since then her symptoms have remained unaltered.

On examination last May (H. E. H. and A. S.) corrected visual acuity of 6/9 was elicited in each eye with no apparent restriction of the peripheral fields. In the central fields were small paracentral scotomata within the 5° circle, relative in the right eye, absolute in the left (2/2000 white object). The optic fundi showed narrowing of the vessels but none of the pigmentation seen in the first case. At the maculæ, however, were small abnormalities: an atrophic, depigmented area in the right eye; one of encysted fluid at the left, corresponding in position to the field defects plotted. The corneæ showed no abnormality; but in the anterior cortex of both lenses were a number of snowflake opacities.

**Case 3.**—A woman of 66 had a history of arthritic symptoms for four years. She had been under treatment with chloroquine sulphate (400 mg. per day) for three years and complained of visual disturbance six months before we saw her. At that time she was aware of a " fog before the eyes " which seemed to be " just over what I look at ", and examination (Mr. R. Jaffe) showed her vision with spectacles to be reduced to 6/9 in the right and 6/12 in the left eye. The visual fields showed ill-defined defects and both corneæ the characteristic corneal deposits. Chloroquine sulphate was stopped at this time and cortisone eye-drops substituted.

Vision had remained unaltered up to the time of the further ocular examination last May (A. S. and H. E. H.) which revealed maximum visual acuity in the right eye of 6/18, in the left of 6/12. The right peripheral field showed a severe upper temporal defect extending to fixation, and in the left eye restriction was apparent in both upper quadrants. Cooperation was inadequate for examination of the central fields. The optic fundi showed narrowed vessels, with an œdematous area at the right macula, but no abnormal pigmentation. Both corneæ showed the pigmented lines seen in the late stage of chloroquine keratopathy, and both lenses early cataracts of a senile type.

### Discussion

The fundus appearances in case 1 were obviously those of a form of " retinitis pigmentosa ", atypical in the actual appearance of the pigment, showing no aggregation around the vessels and evidently acquired. At that time we did not think that the condition was associated with treatment, although this possibility was considered, as was that of an unusual manifestation of lupus erythmatosus. Because the field changes might indicate a quite separate lesion involving the chiasma, the patient, with the cooperation of Dr. R. E. Kelly, was transferred to Maida Vale Hospital for investigation. No evidence, clinical, radiological, or serological, of an intracranial lesion was discovered. In view of these findings further treatment with antimalarial drugs was felt to be unwise.

The condition in case 2 was evidently less serious than in case 1; but this second association of narrowed retinal vessels, macular lesions and scotomatous vision with chloroquine treatment made it more likely that the condition was iatrogenic.

Case 3 provided further evidence of this association. From the absence of pigmentary retinal changes, it appeared to be of intermediate severity, although the extension of the field defect to the fixation point in the right eye had resulted in greater loss of central vision.

The important common features of the ocular disturbance in these cases are the macular lesions and narrowed retinal vessels, and the scotomatous vision and field defects to which they give rise. The retinal pigmentation in case 1 (and in a later case, Y.Z., seen by H. E. H.) may well represent a further stage of the retinopathy, which begins with narrowing of the arteries and retinal œdema, and later progresses to pigmentation both peripherally and centrally.

We do not know whether the lesions are permanent, but their course to date does not suggest that spontaneous improvement is likely.

In these three cases the retinal changes described seem to have arisen after, respectively, $3^1/_2$, $2^3/_4$, and 3 years' treatment with chloroquine compounds; and their severity shows some correspondence to the dose used. In all, the dosage had been between 100 and 600 mg. daily. Withdrawal of the drug has not been followed by improvement, so far; but the lesions have ceased to progress. It seems improbable, therefore, that the changes are due to the underlying disease process, more especially since this has (in case 1) relapsed severely on the withdrawal of treatment. We think the condition more likely to result from administration of the drug.

The known general effects of chloroquine compounds give little ground for the belief that they can provoke a retinal vascular response similar to that seen in our patients. Much the same could be said, however, in respect of quinine, which is known to produce comparable retinal damage by a similar mechanism. Moreover, such a vascular response is by no means specific to quinine, occurring not only with its related compounds (ethylhydrocupreine, quinidine, but also with salicylic acid, filix mas, tryparsamide, and other substances. Idiosyncrasy may well play a part in the retinal response to the synthetic antimalarials, as with quinine; for only a small proportion of cases are affected.

Among the published descriptions of visual disturbance resulting from synthetic antimalarial drugs, we have found no cases with the features seen in our patients; but it seems very likely that the case reported by Sternberg and Laden (1959), in which visual loss associated with macular degeneration was seen after four and a half years' intermittent treatment with chloroquine, was of the same type; and the severe field loss reported by Goldman and Preston (1957) after long-continued chloroquine treatment is suggestive of a similar mechanism.

Our attempts to produce, in rabbits, a retinal lesion with chloroquine sulphate were unsuccessful.

Chloroquine is fairly toxic to the rabbit when given intravenously: 20 mg. per kg. killed all three rabbits tested; two out of three animals died soon after the injection of 15 mg. per kg., and two out of six died after injections of 12·5 mg. per kg. The five survivors of this series of twelve animals showed no ophthalmoscopic lesion after five days, and a further injection of 12·5 mg. per kg. in four of them after twenty-four hours' fasting was also without effect.

These negative findings need to be assessed against what is known of experimentally induced retinal damage in the rabbit by single intravenous injections of non-toxic doses of different agents. Retinal damage with pigmentary disturbance is readily produced in the rabbit by sodium iodate (Sorsby 1941) and the diaminodiphenoxyalkanes (Sorsby and Nakajima 1958)—both of which have been used in a modified form therapeutically in man. In addition there are several agents which have induced retinal lesions in animals, but which have not been used in man: sodium iodoacetate (Noel 1951), dithizone (Butterini et al. 1953), and sodium fluoride (Sorsby and Harding 1959).

Chloroquine, therefore, does not behave in the same way as either of these groups but would appear to be more akin to piperidylethylchlorophenothiazine (N.P. 207, Sandoz). This substance, a tranquilliser allied to chlorpromazine, is known to have produced retinal damage with pigmentation in patients under psychiatric treatment, but it did not do so in animals (Burian and Fletcher 1958).

The clinical findings suggest that the effect of chloroquine and piperidylethylchlorophenothiazine on the human retina is to be ascribed to vascular spasm. This would account for our negative experimental results, since the damage done by retinotoxic agents in the rabbit is clearly the result of a direct effect upon the rod and pigment layer in which the blood-vessels are not involved.

### Conclusions

On present evidence, the retinopathy here described results from treatment with chloroquine compounds. As the corneal changes known to be produced by chloroquine occur also with other synthetic antimalarials, it is possible that these, too, may cause retinal damage—at any rate when they are given in the dosage needed for the treatment of arthritis or lupus erythematosus.

In the absence of less toxic alternatives, it is unlikely that treatment of these diseases with antimalarial drugs will be discontinued. Nevertheless it appears prudent not to prolong such treatment unnecessarily. Courses should perhaps be short, and they should be controlled by periodic ophthalmic examination.

The fourth case mentioned above (Y.Z.) is one discussed by the Section of Dermatology of the Royal Society of Medicine last May and will be published in the Society's *Proceedings*. In the onset of hemeralopia and scotomatous visions and the presence of field defects and retinal changes there was a close resemblance to case 1 above, but the condition was more severe, the patient being virtually blind.

We are indebted to Mr. R. Jaffe for details of his initial examination of case 3; and to Dr. R. E. Kelly for the neurological assessment of case 1, who was referred to us by Dr. John Morgan. The fourth patient is under the care of Dr. G. C. Wells, through whose courtesy she was examined.

REFERENCES

Alving, A. S., et al. (1948) *J. clin. Invest.* **27**, suppl. 60.
Bagnall, A. W. (1957) *Canad. med. Ass. J.* **77**, 182.
Burian, H. M., Fletcher, M. C. (1958) *A.M.A. Arch. Ophthal.* **60**, 612.
Butterini, U., Grignolo, A., Baronchelli, A. (1953) *G. Clin. med.* **34**, 1253.
Dame, L. R. (1946) *Amer. J. Ophthal.* **29**, 1452.
Freedman, A., Bach, F. (1952) *Lancet*, ii, 321.
Goldman, L., Preston, R. H. (1957) *Amer. J. trop. med.* **6**, 654.
Hobbs, H. E., Calnan, C. D. (1958) *Lancet*, i, 1207.
Leopold, I. H. (1958) Survey of Ophthalmology; vol. III, p. 538. Baltimore, U.S.A.
Marx, R. (1959) Personal communication.
Noel, W. K. (1951) *J. cell. comp. Physiol.* **37**, 283.
Page, F. (1951) *Lancet*, ii, 755.
Sorsby, A. (1941) *Brit. J. Ophthal.* **25**, 58.
— Harding, R. (1959) In the press.
— Nakajima, A. (1958) *Brit. J. Opthal.* **42**, 563.
Sternberg, T. H., Laden, E. (1959) *A.M.A. Arch. Derm.* **79**, 116.
Zeller, R. W., Deering, D. (1958) *J. Amer. med. Ass.* **168**, 2263.

## EVALUATION OF TREATMENT OF WARTS BY HYPNOSIS

A. H. C. SINCLAIR-GIEBEN
M.D. Amsterdam, M.B. Edin., M.R.C.P.E., Dip. Psych. E.
LECTURER, DEPARTMENT OF MENTAL HEALTH, UNIVERSITY OF ABERDEEN

DEREK CHALMERS
M.B. Aberd.
REGISTRAR, DEPARTMENT OF DERMATOLOGY, ABERDEEN ROYAL INFIRMARY

MANY workers have described the treatment of warts by hypnotic suggestion, but its value remains uncertain. For this there are several reasons: (*a*) the number of cases treated has been small; (*b*) there have been no controls (except in the investigation by Bloch 1927); and (*c*) spontaneous recovery is common. The present experiment was designed with these three criticisms in mind.

### Material and Methods

In a pilot study 6 patients were freed from their warts within three months by medium deep hypnosis. The remaining patient, who was mentally defective, failed to respond. 4 of these patients had already had various forms of physical treatment for some time without success.

In the main trial all the patients had bilateral and multiple common warts of at least six months' duration,

and only one side of the body was treated—always the side that had more or larger warts. The other half of the body served as a control.

*Hypnotic Techniques*

The hypnosis achieved was graded as:

1. *Deep.*—When asked to do so, the patient will open his eyes, walk about, and talk. Hallucinations can be induced. Post-hypnotic suggestion is effective, and there is complete amnesia.

2. *Medium deep.*—Amnesia is partial or complete and post-hypnotic suggestion is effective. But when asked to open his eyes the patient wakens, and hallucinations cannot be induced.

3. *Light.*—Cataplexy and/or anæsthesia can be induced; but no amnesia can be achieved and post-hypnotic suggestion is ineffective.

Post-hypnotic suggestion was used as a guide to the probable efficacy of treatment. Under hypnosis the patient was instructed, for example, that, after awakening, he would open the door when the examiner blew his nose. If he did so, we assumed that hypnosis would be effective in treating warts.

*Techniques of Induction*

All the patients were hypnotised by one of us (S.-G.) The method of induction followed well-established lines—relaxation, darkness, eye fixation, and repetitive commands. Once a state of hypnosis was induced, two suggestions were given: 1, that the warts on one side (usually hand) would disappear; 2, that on awakening the patient would perform some specified action as described.

Patients varied in their response to hypnosis; some (often the sceptical) responded with medium to deep hypnosis; others (often the overanxious or gullible) were resistant. Others again who were resistant at first responded well later. The most responsive patients were usually of at least average intelligence, and in the second or third decades of life.

The procedure was without fuss: in the course of a brief explanation the words " suggestion " or " relaxation " were used rather than " hypnosis ", to avoid the anxiety this can engender.

## Results

Of 14 patients so treated, adequate depth could be reached in 10, and the results in these are shown in the table. The time taken for cure on the treated side was between five weeks and three months. In the other 4, whose hypnosis was only light, no benefit was obtained.

RESULTS OF TREATMENT

| Patient | Sex | Side treated | Improvement in warts on side treated | Improvement in warts on other (control) side | Level of hypnosis | Posthypnotic suggestion |
|---|---|---|---|---|---|---|
| A | M | L | Cured except for big one which is fading | None | Medium | Present |
| B | F | R | Cured | None | Medium | Present |
| C | M | R | Cured | None | Medium | Present |
| D | F | L | Cured | None | Medium | Present |
| E | F | R | Cured except for big one which is fading | None | Deep | Present |
| F | M | L | Cured | None | Medium | Present |
| G | M | L | Cured | None | First light, then medium | Present |
| H | M | L | Cured | Disappeared 6 weeks later | Very deep | Present |
| J | F | R | Cured | None | Medium | Present |
| K | M | L | None | None | Medium | Absent |

If the original 7 from our pilot study are included, 15 out of 21 *consecutive* patients could be hypnotised to an adequate depth. Only 2 cases failed to return after one session of hypnosis: one could not be hypnotised at all and the other only lightly.

Our two main conclusions were:

1. *Cure can be achieved by hypnosis.*

The perfectly matched controls provide indisputable evidence. Any immediate improvement observed was always on the treated side. In 1 patient the untreated side showed spontaneous disappearance six weeks after the treated side had been cured. In this patient exceptionally deep hypnosis had been achieved with induced skin changes, amnesia, and hallucinations.

2. *The hypnosis must reach a certain depth.*

Those patients who lost their warts had all shown post-hypnotic suggestion—i.e., after awakening they had performed actions suggested to them. In those who got no benefit such suggestion had failed.

## Discussion

The necessity for adequate depth of hypnosis explains why ordinary suggestion is effective only in a proportion of cases: Bloch (1927), for example, found that hypnosis had been successful in 25–44% of patients, depending on the investigator. Our series has shown that cure will be achieved in all cases where some other post-hypnotic suggestion has been induced. This fits in with Asher's view that the patients who respond best are those who have been most deeply hypnotised.

Results with physical treatment applied at fortnightly intervals have been equally good, and the advantages of hypnosis have to be weighted against the possible disadvantages.

*Advantages*

1. In our series, warts appeared to shrivel up and disappear without leaving a scar—even big warts did so. Therefore, large warts, particularly surrounding the nailbed or on the fingers, would be specially suitable for hypnotic treatment.

2. Treatment is painless.

3. There are no dangers of hypersensitivity to local applications or local anæsthetics.

4. In warts on the fingers manual workers are not hampered by raw areas requiring dressings.

5. There is no need for special apparatus—e.g., liquid nitrogen, which requires quite elaborate arrangements.

6. Hypnosis is particularly suitable for certain types of warts which are otherwise difficult to treat—e.g., plantar warts and numerous multiple warts.

*Disadvantages*

1. There is still considerable public and professional prejudice against hypnosis, and the practitioner may suffer in reputation. Some patients refuse such treatment. In our series this happened only twice—but then we used the word " suggestion " rather than hypnosis.

2. Hypnosis takes time and cannot be done in a hurry. In large wart clinics this might be overcome by hypnosis of 20 or 30 patients simultaneously.

3. Many people think that hypnotic skill is difficult to acquire—and possible to only a few. Actually, almost anyone can acquire the techniques from a little reading and demonstration by a competent hypnotist.

4. Some feel that the patient/doctor relationship might be disturbed. We have found that, on the contrary, after several hypnotic sessions a relationship vaguely resembling a transference situation is established. Naturally, great care must be

taken: for instance, no demonstration of hypnosis to other doctors should be given without the patient's consent.

*Ætiology of Warts*

The cause of warts is not as clear as some people suppose. The common assumption that a virus is responsible is based on the work of Variot (1894) and Ciuffo (1907), but these authors and others have shown only the presence of a virus by inference, inasmuch as they managed to transmit warts by the filtrate of ground-up warts. Inclusion bodies have been demonstrated in certain warts (Lyell 1950), but this in itself cannot be taken as proof of a virus. Pillsbury et al. (1956) cite the Koebner phenomenon (i.e., the appearance of lesions at the site of injury) as proof of the infective nature of warts, but this phenomenon is seen in other skin conditions, such as lichen planus and psoriasis, where no infective theory stands up to simple tests.

The suggestion has been made that warts are nævis-like structures (Ewing 1940). If this were so, one would expect them to be inherited rather than transmitted. Another possibility is that the wart is an epidermoma similar to the Shope papilloma of cotton-tailed rabbits (Shope and Hurst 1933). This could account for their transmissibility. But the Shope papilloma can be induced to grow in any tissue (e.g., muscle), provided some epidermis is included, whereas this cannot be done with simple wart tissues.

If the cause is in fact a virus, we must conclude that hypnosis can in some way protect body tissues against infection. Some further simple experiments suggest themselves—e.g., an attempt at transmission of warts by injection of wart tissue in one limb, whilst the other limb, similarly injected, is protected by hypnosis. Used in such ways hypnosis might prove a useful new means of investigation.

**Summary**

14 cases of warts were treated by hypnosis. It was suggested to the patient that the warts on one side of the body (the worst affected) would disappear. The other side served as a perfectly matched control.

In 9 of the 10 patients in whom deep or moderate hypnosis was achieved, the warts on the "treated" side disappeared while those on the control side remained unchanged.

This treatment was effective in *all* cases where the patient was hypnotised deeply enough to perform, on awakening, some action that had been suggested to him.

Hypnotic suggestion confined to one side of the body could prove a useful means of investigating the ætiology of various conditions.

We must thank Prof. Alexander Kennedy for introducing one of us to hypnosis and for his stimulating interest; Prof. W. M. Millar for his interest, his helpful criticism and his permission to conduct this trial; Dr. Reginald Bailey, for allowing one of us to treat some of his patients in Gogarburn Hospital; Dr. T. E. Anderson, for his permission to treat his patients; Dr. Alan Lyell for his interest and his helpful criticism in the preparation of this paper; Mr. William Topp for assistance in the photography; and finally, the patients for their cooperation.

REFERENCES

Asher, R. (1956) *Brit. med. J.* i, 309.
Bloch, B. (1927) *Klin. Wschr.* **2**, 2271.
Ciuffo, G. (1907) *G. ital. Mal. vener.* **48**, 12.
Ewing, J. (1940) Neoplastic Diseases; p. 500. London.
Jadassohn, J. (1896) *Verh. dtsch. derm. Ges.* **5**, 497.
Lyell, A. (1950) Ætiology of Infective Warts. M.D. thesis, Cambridge.
Pillsbury, D. M., Shelley, W. B., Kligman, A. M. (1956) Textbook of Dermatology.
Shope, R. E., Hurst, E. W. (1933) *J. exp. Med.* **58**, 607.
Variot, G. (1894) *J. Clin. Therap. Inf., Paris*, **2**, 529. Cited by Jadassohn (1896).

# ACETYLCHOLINE, ADRENALINE, AND THE HEART

C. S. McKENDRICK
M.A., M.D. Cantab., M.R.C.P.
CONSULTANT PHYSICIAN
A. M. GODFREY
M.B. Lpool
RESEARCH FELLOW
THE LIVERPOOL REGIONAL CARDIAC CENTRE,
SEFTON GENERAL HOSPITAL, LIVERPOOL

DURING the past ten years a series of interesting and important studies on the mammalian heart have been made by Burn and his associates in the department of pharmacology at Oxford. They first demonstrated that acetylcholine had an inhibitory effect on the beating auricle; and by contrast, if the auricle ceased to beat when fatigued or when poisoned by proguanil ('Paludrine'), acetylcholine in minute amounts would restart it. Associated enzyme studies showed that rabbit auricles actively synthesise acetylcholine, and that the power of an individual auricle to carry out this synthesis was directly parallel with its contractile activity. This last observation was demonstrated also in perfusion experiments on the whole heart (Bülbring and Burn 1949, Burn and Kottegoda 1953, Briscoe and Burn 1954).

As a result Burn presented the hypothesis that the local formation of acetylcholine in heart muscle is responsible for cardiac contraction, and that the action of acetylcholine on the pacemaker initiates the contraction wave through the auricles (Burn 1955).

Other substances occurring naturally in heart muscle have striking effects on cardiac rhythm. Adenosine triphosphate and other nucleotides intimately concerned with cell metabolism have long been known to inhibit cardiac contraction when injected intravenously (Drury and Szent-Györgyi 1929), and indeed attempts have been made to use adenosine triphosphate therapeutically on the basis of this action (Somló 1955).

The catechol amines, adrenaline and noradrenaline, both have a potent and complex effect on cardiac contraction, and their presence in heart muscle has been reliably demonstrated (von Euler 1946, Goodall 1951). To ascertain whether they play a part in the initiation and control of myocardial contraction, we repeated and extended Burn's work on the isolated rabbit auricle.

## Method

The auricles were dissected from freshly killed rabbits and suspended in an oxygenated organ bath containing 50 ml. of Locke's solution at a temperature of 29–30°C. Their contractions were recorded on a revolving smoked drum by a long-armed lever attached under slight tension to the auricles.

Substances for trial were added to the bath dissolved in 1 ml. of Locke's solution, the initial dose usually being 1 μg.

The effect of increasing the concentration consecutively was determined, the strength of the dose being increased tenfold until a definite influence on auricular contraction was demonstrated. After each change had been recorded, the organ bath was washed out with Locke's solution. At least 10 minutes was allowed to elapse after adding any drug to the preparation, and after the subsequent washing out.

As in Burn's original experiment we found that, although there was some variation in performance, isolated auricles were capable of beating continuously for 20–30 hours, and that they could be placed in a refrigerator at 4°C, wrapped in cotton-wool soaked in Locke's solution, for up to 4 days with no apparent impairment of contractility.

To overcome the variations in individual auricles, all experiments were repeated on at least three different hearts.

EXPERIMENTAL RESULTS

| Agent causing auricular inhibition | Auricle started spontaneously after washing out | Auricle restarted by acetylcholine | Auricle restarted by adrenaline and noradrenaline |
|---|---|---|---|
| Acetylcholine | Always | .. | 4 out of 4 experiments (added to bath containing acetylcholine) |
| Fatigue | .. | 5 out of 12 experiments | 10 out of 10 experiments |
| Proguanil | Never | 4 out of 11 experiments | 8 out of 9 experiments |
| Adrenaline and noradrenaline | 2 out of 6 experiments | 0 out of 4 experiments (added to bath containing adrenaline) | .. |
| Adrenolytic agents (phentolamine, piperoxane, ergotamine, dibenamine) | 2 out of 42 experiments | 0 out of 13 experiments | 26 out of 27 experiments |
| Atropine | 1 out of 9 experiments | 2 out of 4 experiments | 4 out of 4 experiments |
| Mecamylamine and dibutoline | 8 out of 24 experiments | 5 out of 8 experiments | 8 out of 8 experiments |
| Pempidine | Always | .. | .. |

## Results

Our results are summarised in the table.

*Action of Acetylcholine*

The work of Burn and his colleagues was confirmed. Acetylcholine, in amounts of 1–100 μg. added to the organ bath containing about 50 ml. of Locke's solution, stopped the actively beating auricle; on washing out the bath and adding fresh Locke's solution the auricle would usually start beating again spontaneously. Conversely, if the auricle stopped beating naturally or was arrested by adding proguanil 4 mg., acetylcholine 1–100 μg. would restart it.

*Action of Adrenaline and Noradrenaline*

Both adrenaline and noradrenaline in amounts of 1–100 μg. had the same action as acetylcholine on the auricle arrested by fatigue or by proguanil; indeed in our experiments they restarted the auricle more often than acetylcholine itself.

Adrenaline and noradrenaline also promptly restarted the auricle which had been inhibited by acetylcholine.

The auricle could only be stopped by adrenaline in extremely large amounts (about 3 mg.); in these circumstances the auricle contracted very firmly and only occasionally restarted after it was washed out. Acetylcholine would not restart it.

*Action of Adrenolytic Agents*

To see whether an attempt to abolish or reduce adrenaline activity in the muscle affected its contractility, several adrenolytic agents were tried. These all stopped the beating auricle, but the amount needed to stop different auricles varied greatly. Sometimes 30–100 μg. would suffice, but at other times up to 2 mg. had to be added before the auricles ceased beating.

The range of dosage was :

| | |
|---|---|
| Phentolamine ('Rogitine') | 50 μg.–2 mg. |
| Piperoxane | 20 μg.–2·6 mg. |
| Ergotamine tartrate | 100 μg.–1·9 mg. |
| Dibenamine | 2 μg.–3 mg. |

When the auricles were stopped by any of these adrenolytic agents they remained inactive, and could not be revived by washing out the preparation.

No auricle stopped by an adrenolytic agent could be restarted by adding acetylcholine however great the quantity. But by contrast these auricles could always be restarted by adrenaline or by noradrenaline in amounts of 1–100 μg.

*Action of Acetylcholine Antagonists*

In view of this interesting relation between adrenolytic agents and the catechol amines, we attempted to reduce or abolish acetylcholine activity in the preparation.

Hyoscine and tubocurarine failed to stop the auricle beating.

Atropine sulphate in the very large dosage of 15–35 mg. gradually over several hours caused the auricle to stop beating. After arrest with atropine, acetylcholine would sometimes, but not always, restart the auricle. Adrenaline and noradrenaline effectively restarted it each time, even when acetylcholine had failed.

Various ganglion-blocking agents were tried also. Hexamethonium bromide failed to stop the auricle, but mecamylamine hydrochloride in the large dosage of 10–100 mg. did so. After arrest with mecamylamine the auricles were restarted by acetylcholine in half the experiments, but they were always restarted by adrenaline or noradrenaline. Sometimes the auricles restarted spontaneously after mecamylamine arrest when the Locke's solution was changed.

Dibutoline sulphate, which also has cholinergic blocking properties, acted in the same way as mecamylamine, stopping the auricle in the large dosage of 10–100 mg. Both acetylcholine and the catechol amines restarted the dibutoline-arrested auricles, the catechol amines more frequently than acetylcholine.

Pempidine hydrogen tartrate in a dose of 100 mg. also stopped the auricles, but they always started again spontaneously after washing out the preparation.

## Discussion

The isolated rabbit auricle is a most valuable biological preparation in that it is simple to set up and manage, and its response is easy to record. But it carries the grave disadvantages of any isolated organ preparation; its environment is artificial, and the actual physical and biochemical state of the tissue is unknown. One must remember therefore that conclusions drawn from this study are not necessarily valid if applied to the intact animal; they only provide an indication of possible mechanisms.

Our results indicate, however, that the catechol amines, adrenaline and noradrenaline, have an equal or even more potent effect than acetylcholine in the initiation of auricular contraction after inhibition with proguanil or acetylcholine, or cessation by fatigue. They show also that if adrenolytic agents are added to the preparation, the auricles stop and acetylcholine does not restart them. Until adrenaline or noradrenaline is reintroduced into the system no contraction will occur.

So far we have been unable to demonstrate a parallel cardiac inhibition produced by blockade of acetylcholine

activity which would be reversed solely by acetylcholine while remaining unaffected by the catechol amines.

The exclusive control of acetylcholine over cardiac rhythmicity is therefore unlikely, and, as has been shown, isolated heart-muscle liberates not only acetylcholine but adrenaline and noradrenaline (Burn 1956).

Our studies suggest that cardiac rhythmicity is maintained by the local production of both acetylcholine and the catechol amines, acting either in concert or in antagonism.

The maintenance of balanced contractions must take place through control of the cellular action-potential. Acetylcholine shortens the period of repolarisation, and Burn has suggested that it does this by increasing the permeability of the cell membrane to the outward movement of potassium ions.

It is interesting that Webb and Hollander (1956) demonstrated that adrenaline lengthens the period of repolarisation, and Grob et al. (1957), in a study of potassium-ion movement in man, showed that the forearm muscles appeared to take up potassium from the blood-stream when adrenaline was given intra-arterially, and to release potassium when acetylcholine was given.

We suggest therefore that the rhythmic contraction of cardiac muscle is due to acetylcholine and the catechol amines, produced locally and acting antagonistically, in altering the permeability of the muscle-cell membrane and the movement of potassium in and out of the cell. Certainly the direct antagonism of the catechol amines to the cardiac inhibition produced by acetylcholine in these experiments supports such an explanation. To what extent blood-borne hormones and cardiac innervation affect this situation in the intact animal is a further problem.

**Summary**

Previous work has indicated the importance of acetylcholine in the control of rhythmic cardiac contractions. In further experiments on isolated rabbit auricles the importance of the catechol amines in initiating and maintaining cardiac activity is shown.

After auricular arrest with adrenaline-blockading substances, contractions are restored only by the addition of adrenaline or noradrenaline. Both these substances were more potent than acetylcholine in overcoming cardiac arrest produced by fatigue or by substances such as proguanil (' Paludrine ') or atropine, which are known to depress the activity of acetylcholine.

Thus the catechol amines as well as acetylcholine may play an important part in the initiation and control of myocardial rhythmicity.

Our thanks are due to the United Liverpool Hospitals research committee, whose generous financial grant made the completion of this work possible; to Prof. B. G. Maegraith and the council and staff of the Liverpool School of Tropical Medicine not only for provision of laboratory space and equipment but also for constant helpful advice and encouragement; and to Dr. T. R. Littler who assisted in this work.

REFERENCES

Briscoe, S. M., Burn, J. H. (1954) *J. Physiol.* **126**, 181.
Bülbring, E., Burn, J. H. (1949) *ibid.* **108**, 508.
Burn, J. H. (1955) Lectures on the Scientific Basis of Medicine; vol. III, p. 127. London.
— (1956) Functions of Autonomic Transmitters; p. 34. Baltimore.
— Kottegoda, S. R. (1953) *J. Physiol.* **121**, 360.
Drury, A. N., Szent-Györgyi, A. (1929) *ibid.* **68**, 213.
Goodall, M. (1951) *Acta physiol. scand.* **24**, suppl. 85, 1.
Grob, D., Liljestrand, A., Johns, R. J. (1957) *Amer. J. Med.* **23**, 340.
Somló, E. (1955) *Lancet*, i, 1125.
von Euler, U. S. (1946) *J. Physiol.* **105**, 48.
Webb, J. Z., Hollander, P. B. (1956) *Circulation Res.* **4**, 332.

# RENAL TUBULAR DEGENERATION
## ELECTRON MICROSCOPY IN ISCHÆMIC ANURIA

O. Z. DALGAARD
M.D. Copenhagen
ASSISTANT PHYSICIAN,
DEPARTMENT 3, AND THE CENTRAL CLINICAL LABORATORY,
MUNICIPAL HOSPITAL, COPENHAGEN

K. J. PEDERSEN
M.Sc. Copenhagen
UNIVERSITY DEMONSTRATOR,
INSTITUTE OF GENERAL ZOOLOGY AND BIOPHYSICAL INSTITUTE,
UNIVERSITY OF COPENHAGEN

As early as 1929, Richards studied microscopically the nephrons of frogs poisoned with nephrotoxins. The glomerular circulation and filtration were apparently normal, but the entire filtrate was reabsorbed in the tubules, resulting in anuria. Richards concluded that the reabsorption of the glomerular filtrate in the tubules was caused by the osmotic pressure of the serum-proteins.

Studying the " crush syndrome ", Bywaters and Dible (1942) and Bywaters (1944) observed a tubular failure correlating with the histological lesions, which were mainly tubular: " There may be excessive and unselective reabsorption of the glomerular filtrate through the tubules, in other words leakage back into the blood stream."

Lucké (1946) and Mallory (1947) observed that the tubular lesions were common to a variety of conditions accompanied by acute reversible renal insufficiency—a condition in which renal function can be completely recovered over a period of weeks or months.

Oliver et al. (1951) and Oliver (1953) isolated entire nephrons by a technique of microdissection, which enabled them to provide a three-dimensional picture of the long vulnerable tubule. They showed that the tubular lesions consisted of scattered foci of epithelial degeneration, necrosis, and dissolution of the basement membrane, throughout the entire course and involving any segment of the tubule.

Biopsy studies of the kidney in acute renal failure have been performed on routine stained sections by light microscopy by

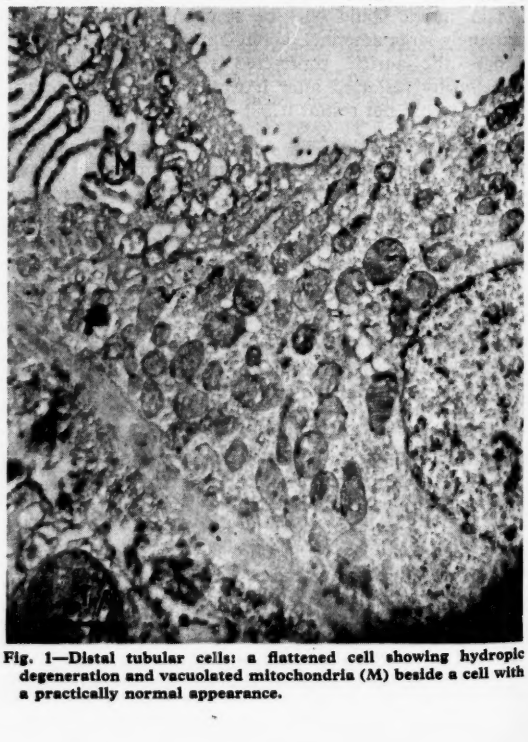



**Fig. 1—Distal tubular cells: a flattened cell showing hydropic degeneration and vacuolated mitochondria (M) beside a cell with a practically normal appearance.**

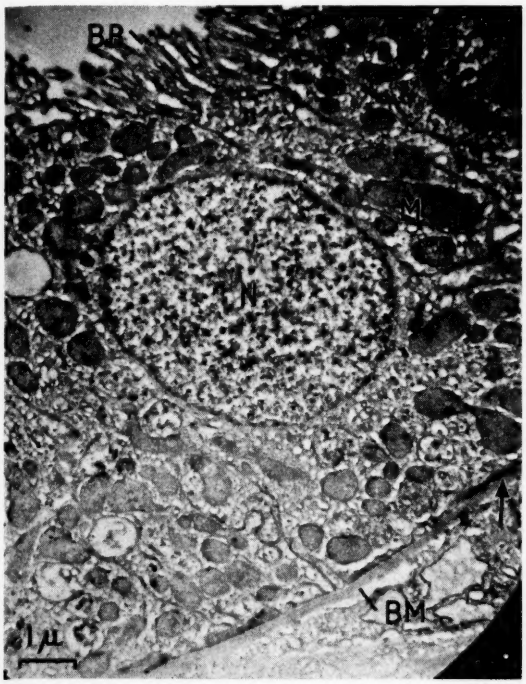



**Fig. 2—Proximal tubular cells (N nucleus, BB brush border, BM basement membrane). The brush border is partly shed, the mitochondria (M) swollen. An electron-dense layer is deposited against the basement membrane (→).**

Brun (1954), Gormsen et al. (1955), and Brun and Munck (1957). The most impressive general observation was the contrast between the moderate structural changes and the complete functional breakdown.

In this preliminary study, the various structural lesions of the renal tubule were examined by the electron microscope, using renal-biopsy material (Iversen and Brun 1951) from a patient with acute ischæmic anuria.

The biopsy specimen was quickly cut in two: one part was used for light microscopy, and the other was cut into small cubes which were fixed for four hours in isotonic osmium tetroxide solution buffered to pH 7·2, dehydrated in 70%, 95%, and absolute alcohol and cast in prepolymerised methyl-butyl-methacrylate (1:20) at 45° (Rhodin 1954). Sections were cut with a glass knife on Sjøstrand's ultramicrotome. The sections were collected on copper grids, covered with a carbon film, and examined in an R.C.A. electron microscope (EMU 2 B). A section 1 $\mu$ thick was also cut from the same block, for examination by phase-contrast microscopy, so that the same glomerulus, for example, could be observed by the two methods.

## Case-report

A woman of 64 had had cerebral thrombosis 12 years previously, with rapid and almost complete remission. A year ago she was admitted to a neurological department for atrophic encephalopathy (? arteriosclerotic) and symptomatic epilepsy. She was readmitted for acute barbiturate poisoning after attempted suicide. She had been seen last by her family three days before admission. She was comatose, reflexes could not be elicited, there was slight tachypnœa, the hands were slightly cold, and pressure markings were observed on the back and heels. Temperature was 102·1°F (38·9°C) and blood-pressure 100/70 mm. Hg. Her condition improved after blood-transfusions.

On the third day the urine volume fell to 35 ml. in 24 hours and the serum-creatinine rose from 1·3 to 6·0 mg. per 100 ml. Renal biopsy was performed on the fourth day (serum-creatinine 5·9 mg. per 100 ml., 24-hour urine volume 90 ml., 24-hour creatinine clearance 0·36 ml. per min., serum-urea 272 mg. per 100 ml., serum-potassium 4·1 mEq. per litre).

Hæmodialysis was carried out without complications on the sixth day. In the course of the dialysis, the serum-urea fell from 487 to 112 mg. per 100 ml. The patient regained consciousness next day, the 24-hour urine volume gradually increased from this point and the serum urea and creatinine concentrations fell.

On discharge about seven months later, renal function was about 40% normal, measured by the 24-hour creatinine clearance.

## Light Microscopy

Phase-contrast microscopy, using the portions fixed in osmium tetroxide, showed eight glomeruli which were normal in appearance. No definite lesions were seen in the proximal tubules. The distal tubules were somewhat dilated, with flattened epithelium, and in places contained granular casts.

Ordinary light microscopy of the formalin-fixed piece, which was about 7 mm. long and consisted almost entirely of medulla, showed only a few distal tubules, containing rather flattened epithelium. Hyaline casts or hæmoglobin casts were found in several of these tubules. The cortex seemed œdematous.

Cylinders were found in a few of the Henle tubules and collecting tubules. The medulla was otherwise normal.

## Electron Microscopy

*Glomeruli*

Electron microscopy showed the three glomerular components to be normal. The endothelial cells were normal with uniformly placed pores in the thin cytoplasmic layer covering the capillary internally. The basement membrane between the endothelium and the epithelium had a normal central layer which was 0·1–0·2 $\mu$ thick, with normal " cement substance " on both sides.

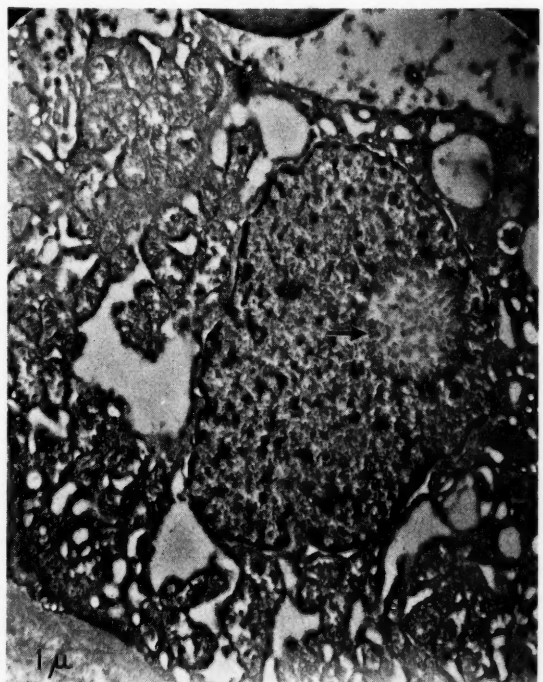



**Fig. 3—Distal tubular cell with pronounced hydropic degeneration, coarsely granulated cytoplasm, vacuolated mitochondria and nuclear pyknosis with strangely radial-striped nucleolus (→).**

The epithelial cells were normal. The cytoplasm was organised into many primary branches. On both sides of each branch secondary branches or "foot processes" arose which interlocked with the neighbouring foot processes and supported the outer aspect of the basement membrane (Dalgaard 1959).

Our electron-microscopy findings that the glomeruli in shock kidney are normal confirm previous light-microscopy studies, both experimental and in patients with ischæmic anuria.

*Tubules*

The histopathological picture in ischæmic anuria has two main characteristics previously demonstrated by light microscopy and elucidated further by electron microscopy.

(1) Degeneration or even necrosis, which can involve the tubular cells over delimited portions from the glomerulus to the collecting tubules.

(2) Disruption of continuity of the tubules (tubulorrhexis), including dissolution of the basement membrane.

The lesions primarily involve the tubular cells, and vary widely in degree from cell to cell, from slight degeneration to frank necrosis and complete disintegration. The lesions show a characteristic focal distribution (fig. 1).

Dilatation of the distal tubules is found in nearly all cases accompanied by corresponding flattening of the epithelial cells, and in most cases also by a similar flattening of the nuclei (Brun and Munck 1957).

*Proximal Convoluted Tubules*

The appearance of the proximal convoluted tubules may be quite normal, even to the complete retention of their fine brush border. At times, however, some of the cells may be slightly swollen, showing rather more granularity, possibly corresponding to the microscopic picture of "cloudy swelling". Frank degeneration and actual necrosis may also be seen.

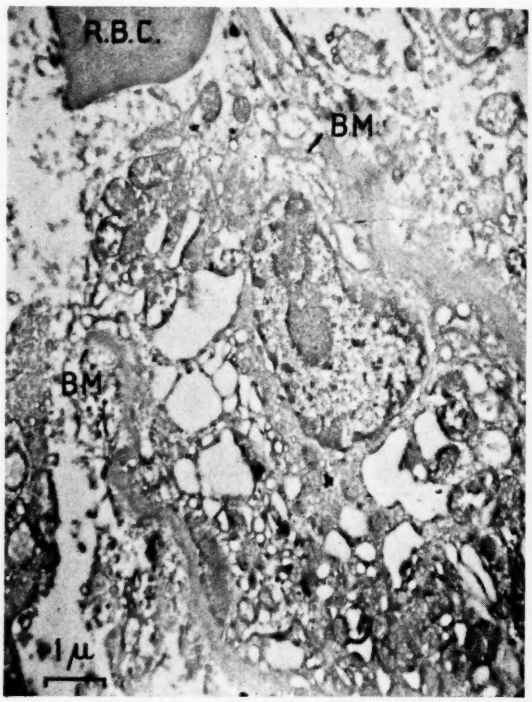



**Fig. 5—Tubulorrhexis in distal tubule. The basement membrane shows a sudden break (BM). Part of a red cell (RBC) is seen in a peritubular capillary.**

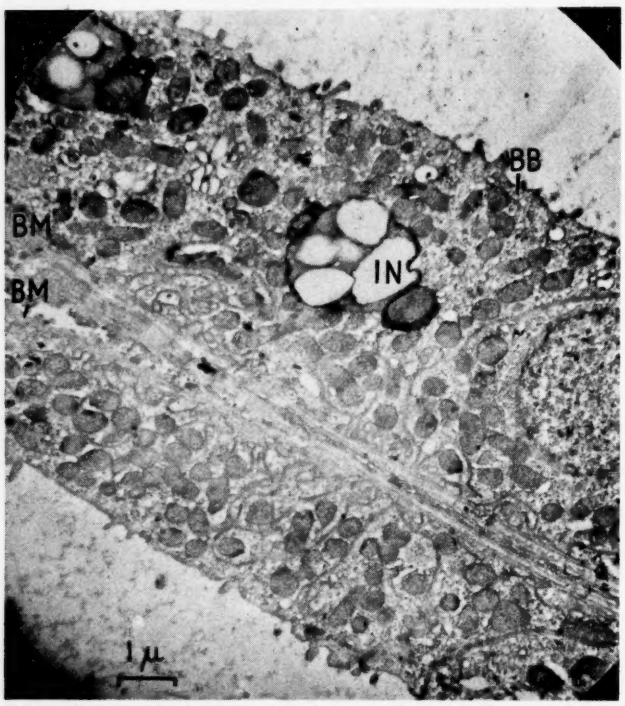



**Fig. 4—Flattened distal tubular cells in two adjacent tubules, with short, broad microvilli (BB), sharply delimited, mutilocular, vacuolated inclusions (IN), and frayed basement membrane (BM) split into fibrils.**

Normally, the ground cytoplasm is divided into compartments (labyrinths) by double membranes, which are closed towards the basement membrane. The compartments are separated from the basement membrane by a non-osmium-impregnated layer.

The ground cytoplasm consists mainly of two components: opaque particles and minute fibrils, which may consist of a single fibril or of a membrane, and which in section have the appearance of an irregular network (Rhodin 1958).

In this case, the ground cytoplasm often showed a coarsely granulated appearance, with many small and large vacuoles without distinct boundaries, scattered throughout the cytoplasm.

The mitochondria are normally surrounded by an outer double membrane and possess a system of inner double membranes (cristae mitochondriales). The matrix structure is diffusely granular (Rhodin 1958). In this case, the mitochondria were found to be more swollen at first, with increasing conversion of the cristae to a homogeneous, finely granular structure which resembled the matrix (fig. 2). Those double membranes which have remained may be normal in appearance and length, or be thickened. "Swelling" may cause the double membranes to separate more or less completely from the outer membrane. The matrix then acquires a coarsely granulated appearance, with a diffuse spread of many small vacuoles without distinct boundaries.

More pronounced changes then appear in the form of increasingly diffuse waterlogging of the mitochondria and disintegration of their outer membrane.

There may be very pronounced changes in the cell nuclei, shown either as a " chromatolysis ", in which the chromatin granules are scanty except peripherally at the nuclear membrane and the nucleolus, or as a " pyknosis ", in which coarse, closely packed granules are seen in a condensed cell nucleus.

In diffuse waterlogging, the organelles are seen to be severely damaged. They are disintegrating and in dissolution, so that the cell consists of coarse and fine dispersed granules and fragments of organelles. The nucleus becomes diffusely waterlogged and swollen, and the nuclear membrane is clearly seen within the hydropic cell, and may show large gaps. This picture corresponds to Robinson's interpretation of the pathological process in most organs, where poor oxygen supply to the cells is followed by cloudy swelling and hydropic degeneration, the essential feature of which is an accumulation of water in the cells (Robinson 1952).

*Distal Convoluted Tubules*

Normally, the cell boundaries in the luminal part of the cell are straight, while in the basal part they show a very complicated course, with the cells interlocking here (Rhodin 1958). The degenerative changes are identical with those in the proximal tubules but more pronounced (figs. 3 and 7).

Some of the flattened tubule cells are pathologically changed, their nuclei showing great variation in shape and electron density. Other of the flattened tubule cells are regenerating and have a relatively undifferentiated appearance, and their cell membranes are simple in contour. They contain a few small mitochondria. Large round inclusions are often seen in the cytoplasm of the flattened cells. They are very sharply delimited, often containing multilocular vacuoles as well as a homogeneous substance (fig. 4). The basement membranes are quite frayed or even split in places (fig. 4).

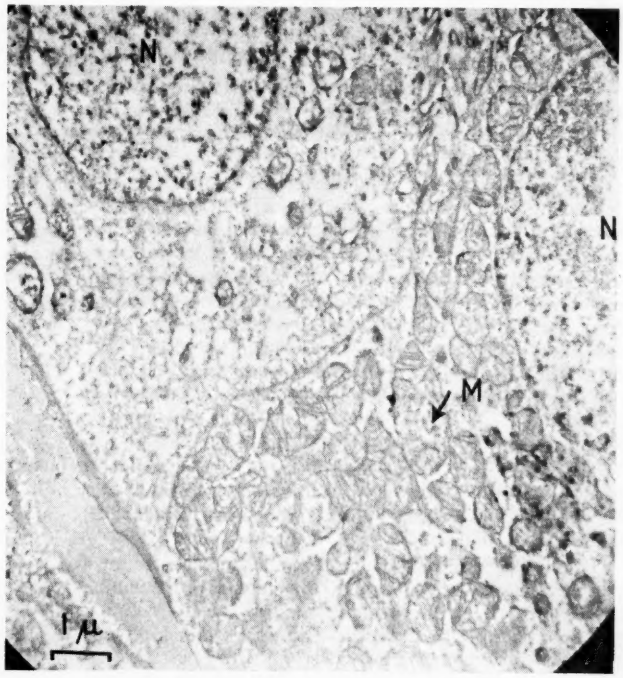



**Fig. 7—Distal tubular cells showing pronounced degeneration: the one with diffuse waterlogging with few mitochondria and cytomembranes, the other with hydropic degeneration and severely swollen mitochondria (M).**

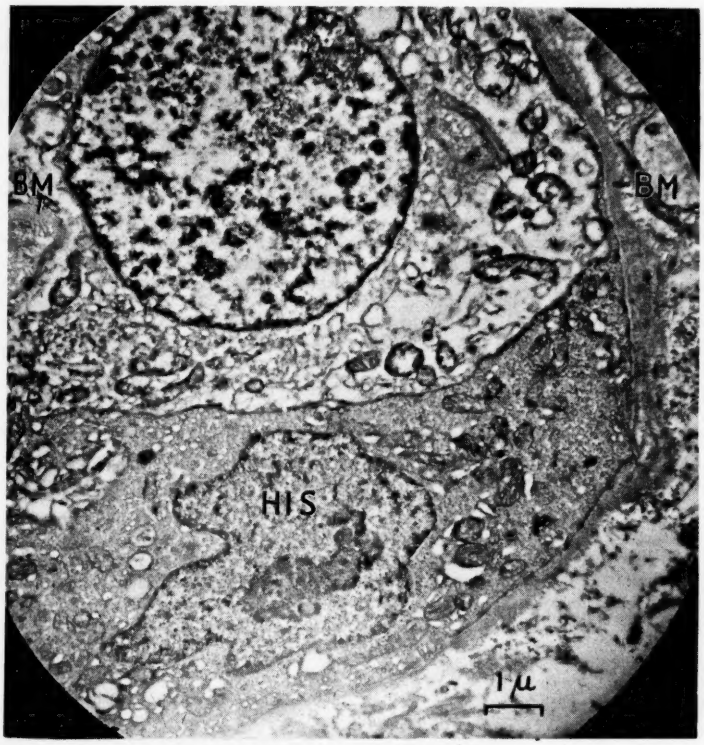



**Fig. 6—Tubulorrhexis in distal tubule. A connective-tissue cell (HIS) is seen sealing a break in the basement membrane (BM).**

*Tubulorrhexis*

This is found in both distal and proximal tubules but is a rather rare phenomenon. The basement membranes may be suddenly interrupted (fig. 5). Elsewhere they are frayed or disintegrated into fibrils (fig. 4), and the epithelial layer disrupted and necrotic. Fig. 6 shows a connective-tissue cell " sealing " a break in a tubule. Occasionally, an amorphous, electron-dense layer is found deposited basally in the cell, possibly an indication of commencing necrosis and the shedding of the cell (fig. 7).

*Collecting Tubules*

Obvious pathological changes are rare in the collecting tubules, and most cells appeared normal.

## Discussion

Our findings agree with and extend those of Oliver et al. (1951) and Oliver (1953), who used the technique of microdissection. The lesions are a patchy or focal distribution of epithelial degeneration and necrosis and are found throughout the entire nephron from the proximal convoluted tubules to the collecting tubules, but particularly in the distal convoluted tubules.

It is remarkable that completely normal cells can be observed side by

side with diseased cells, or even frankly necrotic cells which are about to be shed. A similar focal distribution of the lesions is seen in cerebral ischæmia.

The renal biopsy was performed on the third day of anuria, when, according to Lucké's (1946) investigations, the destructive processes have reached their maximum and regeneration has begun.

The dilatation of the distal convoluted tubules may be caused by casts, producing mechanical blockage, or by occlusion of the lumen, when disrupted points grow together.

The ischæmia may possibly weaken the basement membrane, or the dilatation may be apparent, resulting from the remaining epithelial cells flattening out and spreading over the denuded tubule, just as proliferating cells from an epithelial graft cover a wound surface.

The changes in the basement membrane appear as sudden breaks and as a frayed or disintegrated fibrillar membrane with a disrupted or necrotic epithelial covering. When there is a disruption of the basement membranes, the filtrate may possibly leak back as a result of interrupted flow, caused by casts lying more distally in the nephron.

The leakage of the glomerular filtrate back to the peritubular capillaries through the tubular epithelium can be caused by the osmotic pressure of the blood-proteins, once active transport cannot be maintained by the diseased or dying tubular cells. This may possibly be the most important feature in producing the oliguria.

Investigations are proceeding on the reparative processes in the kidney in acute ischæmic renal failure in man, using biopsy specimens taken later in the course of the disease.

It was not until the introduction of the technique of renal biopsy that the study of these " intimate " cellular details became practicable, both because the structural lesions must be studied at determined intervals during the period of recovery, and because the tissue must be fixed immediately it is obtained, in order to avoid autolysis.

A study will also be carried out with renal biopsies to determine whether the epithelial regeneration and accompanying maturation of the enzymatic function found by Oliver et al. (1951) and Oliver (1953) in the experimental animal is also found in man.

### Summary

Renal biopsy was performed on the third day of anuria in a 64-year-old woman with acute ischæmic anuria. Light-microscopy observations on routine stained sections showed no more than minor lesions; electron microscopy, however, revealed pronounced cellular lesions, with patchy distribution of epithelial degeneration, necrosis, and disruption of the basement membrane, localised from the proximal tubules to the collecting tubule. The lesions were most pronounced in the distal tubules.

This work was aided by grants from the State Foundation for Aid to Scientific Research, Johann and Hanne Weimann's Foundation, the Novo Pharmaceutical Products Fund, and the King Christian X Fund.

REFERENCES

Brun, C. (1954) Acute Anuria. Thesis. Copenhagen.
— Munck, O. (1957) *Lancet*, i, 603.
Bywaters, E. G. L. (1944) *J. Amer. med. Ass.* **124**, 1103.
— Dible, J. H. (1942) *J. Path. Bact.* **54**, 111.
Dalgaard, O. Z. (1959) *J. lab. Invest.* (in the press).
Gormsen, H., Iversen, P., Raaschou, F. (1955) *Amer. J. Med.* **19**, 209.
Iversen, P., Brun, C. (1951) *ibid.* **11**, 324.
Lucké, B. (1946) *Military Surg.* **99**, 371.
Mallory, T. B. (1947) *Amer. J. clin. Path.* **17**, 427.
Oliver, J. (1953) *Amer. J. Med.* **15**, 535.
— MacDowell, M., Tracy, A. (1951) *J. clin. Invest.* **30**, 1307.
Rhodin, J. (1954) Correlation of Ultrastructural Organization and Function in Normal and Experimentally Changed Proximal Convoluted Tubule Cells of the Mouse Kidney. Stockholm.
— (1958) *Intern. Rev. Cytol.* **7**, 485.
Richards, A. N. (1929) *Trans. Ass. Amer. Phycns*, **44**, 64.
Robinson, J. R. (1952) *Proc. roy. Soc.* B. **140**, 135.

### Addendum

Since completing the above paper, a further 6 kidney biopsies from patients with ischæmic anuria have been studied by electron microscopy. Agreement with the observations recorded above has been noted on all essential points.

## A NEW FLOCCULATION TEST FOR DIFFERENTIATING OBSTRUCTIVE FROM HEPATOCELLULAR JAUNDICE

GEORGE K. DAIKOS
M.D. ATHENS
ASSISTANT PROFESSOR OF MEDICINE
PERICLES MATTHEOU
M.D. Athens
MARIA ATHANASIADOU
M.D. Athens
*From the Department of Clinical Therapeutics, Alexandra Hospital Athens University School of Medicine*

NONE of the current laboratory tests for differentiating obstructive from hepatocellular jaundice is entirely satisfactory; and the search for more reliable ones therefore continues. Jirgl (1957), working on the determination of blood-mucoproteins found that the serum of patients with obstructive jaundice became turbid and formed a precipitate on addition of the Folin-Ciocalteau phenol reagent. This was not seen in the sera of patients with other types of jaundice.

We present here an evaluation of this test.

### Material and Methods

We examined 90 sera: 25 from patients with obstructive jaundice; 29 from patients with hepatocellular jaundice; 36 from patients with other conditions, including hæmolytic jaundice and normal pregnancy; and 25 from healthy people.

The test is carried out as follows:

In a test-tube 1·6 ml. serum is added to 4 ml. 0·1*N* KOH. After slight mixing the test-tube is left at room temperature for forty-five minutes, and then 4 ml. 20% sulphosalicylic acid is added. After thorough shaking the tube is left standing at room temperature for another ten minutes; its contents are then filtered. 5 ml. of the filtrate and 1 ml. tungsten-phosphoric acid is then mixed in a centrifuge tube. After ten minutes the tube is centrifuged at 1500 r.p.m. for fifteen minutes. The supernatant fluid is then discarded and the inside of the tube is gently wiped dry of all remaining fluid. The sediment is redissolved in 6·5 ml. 10% $Na_2CO_3$, and 0·5 ml. Folin-Ciocalteau phenol reagent diluted 1/3 in water is added. The contents are well shaken and the result is read.

Jirgl reads the test against a dark background using strong incident light. He makes the result negative (−) when the content of the tube remains clear or slightly bluish; as + when there is a slight turbidity; as ++ when a flocculation occurs; and as +++ if a precipitate forms.

We noticed that in all cases which are considered positive by Jirgl's standards floccules and precipitate appeared after several hours. We therefore read the results twelve hours after completion of the test. We do not use artificial light. We rated the results as +, ++, +++, according to the degree of flocculation and sediment.

### Results

*Obstructive Jaundice*

23 of the 25 cases of obstructive jaundice gave a positive test (table I).

TABLE I—RESULTS OF THE JIRGL FLOCCULATION TEST IN OBSTRUCTIVE JAUNDICE

| Diagnosis | Number of cases | Positive | Negative |
|---|---|---|---|
| Liver neoplasms | 12 | 12 | 0 |
| Lithiasis | 6 | 5 | 1* |
| Hydatid cyst ruptured into the bile-duct | 2 | 2 | 0 |
| Cholangitis | 2 | 2 | 0 |
| Uncertain | 3 | 2 | 1 |
| Total | 25(100%) | 23(92%) | 1(8%) |

* Doubtful.

The first of the 2 negative results was in a woman of 40 who had stones in the common bile-duct. The blood sample was withdrawn eighteen days after the surgical removal of the stones, while she was still jaundiced (serum-bilirubin of 5·8 mg. per 100 ml.; traces of bilirubin in the urine). The second negative test was in a case of a clinically obstructive jaundice in which the cause of the obstruction was not established.

In a man of 40 the obstructive jaundice was caused by rupture of an echinococcus cyst into the biliary system. The test was performed fifty-five days after operation, while slight jaundice was still present (serum-bilirubin 2·1 mg.). The 12 cases of obstruction due to neoplasm, the 2 cases of obstruction due to echinococcus cyst, and the 2 cases of cholangitis with obstructive jaundice all gave positive results.

TABLE II—RESULTS OF TEST IN HEPATOCELLULAR JAUNDICE

| Diagnosis | Number of cases | Positive | Negative |
|---|---|---|---|
| Infectious hepatitis | 14 | 4 | 10 |
| Infectious cholangiolitis | 1 | 0 | 1 |
| Homologous serum jaundice | 5 | 0 | 5 |
| Chronic hepatitis | 3 | 0 | 3 |
| Cirrhosis | 4 | 0 | 4 |
| Toxic hepatitis | 1 | 0 | 1 |
| Uncertain | 1 | 0 | 1 |
| Total | 29(100%) | 4(10%) | 25(90%) |

*Hepatocellular Icterus*

Of 29 cases with non-obstructive jaundice the test was positive in only 3 (table II).

1 of the 3 cases was a woman three months pregnant. The sera of 7 other healthy pregnant women gave negative results.

The jaundice of a woman, aged 40, with infectious cholangiolitis had already persisted for seventy days when she entered hospital. Differentiation between obstructive and hepatocellular jaundice was difficult. Her serum-alkaline-phosphatase was 27 King-Armstrong units and the combined intravenous oral cholangiogram showed only a faint outline of the biliary system and no obstruction. The test was negative; and the subsequent course of the illness justified the diagnosis of infectious cholangiolitis.

In 2 cases of infectious hepatitis and in 2 cases of homologous-serum jaundice in which the tests were performed in the acute phase of the illness while the stools were pale, the results were negative.

TABLE III—RESULTS OF TEST IN MISCELLANEOUS CONDITIONS

| Diagnosis | Number of cases | Positive | Negative |
|---|---|---|---|
| Acute hæmolytic jaundice (favism) | 6 | 0 | 6 |
| Thalassæmia major with jaundice | 2 | 0 | 2 |
| Leishmaniasis | 2 | 1 | 1* |
| Laennec's cirrhosis with jaundice | 4 | 0 | 4 |
| Banti's syndrome | 2 | 0 | 2 |
| Hæmochromatosis | 1 | 0 | 1 |
| Rheumatic fever | 1 | 0 | 1 |
| Pyloric stenosis | 1 | 0 | 1 |
| Infectious mononucleosis | 1 | 0 | 1 |
| Liver neoplasm without jaundice | 2 | 0 | 2 |
| Hydatid cyst of the liver without jaundice | 1 | 0 | 1 |
| Hæmolytic anæmia without jaundice | 1 | 0 | 1 |
| Normal pregnancy | 7 | 0 | 7 |
| Normal individuals | 5 | 0 | 5 |
| Total | 36 | 1 | 35 |

* Doubtful.

*Other Conditions*

Negative results were obtained in the 8 patients with hæmolytic jaundice, in 14 out of the 16 patients without jaundice (table III), in the 7 normal pregnant women, and in the other 5 healthy controls. The 2 control patients whose serum was positive both had leishmaniasis and were under treatment with antimony preparations.

**Discussion**

Our results confirm Jirgl's findings. His test is simple and reliable in the differentiation of obstructive from hepatocellular jaundice: he found it positive in 44 out of 46 cases of obstructive jaundice and negative in all 147 cases of infective hepatitis.

It is not clear what this flocculation represents. The reagents are those which are used for mucoprotein determination. The test does not seem to have any relation to the serum-bilirubin level: 2 of the cases of hepatocellular jaundice had a high serum-bilirubin at the height of their illness, but they gave a negative test. Neither can we find any correlation between Jirgl's test and the blood-cholesterol or the routine liver-function turbidity tests. In cases of long-standing obstructive jaundice, with abnormal liver-function tests, Jirgl's test was negative.

Though we have not performed detailed chemical studies of the precipitate, preliminary observations suggest that it is not mucoprotein. Sera giving positive results remained positive after extraction with ether or chloroform. On the other hand sera from cases of rheumatic fever and neoplasms—whose mucoprotein content is usually much increased—gave negative results.

**Summary**

We have evaluated in a total of 90 sera, the flocculation test described by Jirgl for differentiating obstructive from hepatocellular jaundice.

Flocculation occurred in 92% of sera from patients with obstructive jaundice, but was absent in 90% of sera from patients with hepatocellular jaundice.

Except for 2 cases of leishmaniasis, the test was negative in 16 patients without jaundice, in 7 normal pregnancies, and in 5 other healthy controls.

It is simple to perform, and its use is recommended.

REFERENCE

Jirgl, V. (1957) *Klin. Wschr.* **35**, 938.

## EXPERIENCES WITH LONG-TERM ANTICOAGULANT TREATMENT

J. A. FULLER
M.B. Melb., M.R.C.P.E.
REGISTRAR, CARDIOVASCULAR DEPARTMENT, GENERAL HOSPITAL, NEWCASTLE UPON TYNE

MANY workers have commented on the relative safety of long-term anticoagulant therapy, but the recorded incidence of complications differs widely from one series to another.

Thus Tulloch and Wright (1954) treated 227 patients for a total of 2195 months: they recorded 70 hæmorrhagic complications in 43 (19%) patients, and 1 death from cerebral hæmorrhage. This is an average rate of 3·2 episodes per 100 " patient-months ", or 31 months per patient per episode. McDevitt et al. (1958) noted 51 complications in 2532 " patient-months " (2 episodes per 100 patient-months, or 50 months per patient per complication), while in 121 patients treated for up to five years Keyes et al. (1956) encountered bleeding episodes in 51 (42%) with 3 deaths. Nichol and Borg (1950) found hæmorrhagic complications in 36% of their patients: 2 died

TABLE I—COMPOSITION OF THE SERIES

| Disease | Males | Females | Total |
|---|---|---|---|
| Cardiac infarction | 177 | 27 | 204 |
| Rheumatic heart-disease with embolism | 6 | 2 | 8 |
| Cerebral thrombosis | 3 | .. | 3 |
| Pulmonary hypertension | .. | 1 | 1 |
| Retinal-vein thrombosis | 1 | .. | 1 |
| Total | 187 | 30 | 217 |

TABLE II—AGE-GROUPS OF PATIENTS WITH CARDIAC INFARCTION

| Age (yr.) | 30–39 | 40–44 | 45–49 | 50–54 | 55–59 | 60–64 | 65/69 | Over 70 |
|---|---|---|---|---|---|---|---|---|
| Males | 3 | 15 | 41 | 39 | 40 | 25 | 13 | 1 |
| Females | 0 | 3 | 0 | 6 | 7 | 2 | 7 | 2 |

from cerebral hæmorrhage. Suzman et al. (1955) recorded major hæmorrhage in 15% with two deaths, and Askey and Cherry (1950) in 33% of their series. Manchester (1957) noted complications in only 3% of 200 patients, with no deaths; and at the lower end of the scale Waaler (1957) reported only 1 bleeding episode every 8–9 patient-years. Foley et al. (1955) treated 85 patients for 3628 patient-months with 31 complications and 1 death (0·85 episodes per 100 patient-months, or 117 months per patient per complication), and Bjerkelund (1957) treated 119 patients for 418 patient-years with 53 hæmorrhages in 37 (31%) patients—an average incidence of 1 episode for each 7·9 patient-years of treatment. There were 4 deaths from cerebral hæmorrhage in this series.

Whereas dicoumarol has been the principal anticoagulant in these series, phenindione was used in the recent Medical Research Council (1959) trial. These investigators reported 48 hæmorrhagic complications in 195 patients treated in all for 3178 months—an incidence of 1·5 hæmorrhages per 100 patient-months, or 66 months per patient per complication.

This paper is primarily concerned with the hæmorrhagic complications of phenindione therapy in 217 patients (tables I and II) treated for periods up to three years, to Dec. 31, 1958. Our earlier experiences with ethyl biscoumacetate (' Tromexan ') are not considered.

## Management

Most patients are admitted to hospital, and their long-term dose of phenindione is assessed from their requirements in the ward. Before discharge each patient is advised verbally and by typed instructions about the dangers of anticoagulant therapy. For the past twelve months we have been providing them with an ' Occultest ' outfit to detect microscopic hæmaturia. This we ask them to use three times a week during the early months of treatment, and later, when the dosage is more stable, once or twice weekly.

If the test is positive or the patient notices a small bruise, we advise him to stop the therapy for three days: this is usually sufficient for the trouble to subside. We inquire about such episodes at his next visit to the clinic, and we adjust the phenindione dosage accordingly. With gross or prolonged hæmaturia, extensive bruising, or bleeding from the bowel, or if bleeding does not subside after three days without anticoagulants, we advise the patient to come to hospital.

At first some patients were given vitamin-K tablets to carry with them; but for minor disturbances this is probably not necessary, and for major ones it is safer to see the patient in hospital.

When the patients are fully stabilised we ask them to return at six-weekly intervals for prothrombin estimations; but in the early stages these may have to be performed more frequently, sometimes weekly. After attending the clinic patients receive a letter giving the dose of anticoagulant and the date of their next appointment.

We order a twice-daily dose of phenindione, and we make minor adjustments by omitting one or more doses each week. The aim is to lengthen the one-stage clotting-time to twice that of the control, the prothrombin-concentration then being 12–15%. This level, however, is difficult to achieve without inducing a bleeding tendency in many patients; and in practice a slightly shorter clotting-time is often permitted. Clotting-times are measured by the one-stage method of Quick, using human brain as the source of thromboplastin.

## Mortality and Complications

21 patients died while under treatment, and 18 were withdrawn for other reasons.

*Deaths*

11 patients died suddenly: 4 from further infarction, 2 from heart-failure, and 1 from a ruptured abdominal aneurysm. 1 death was attributed by the general practitioner to cerebral hæmorrhage; but the clinical picture was inconclusive and no necropsy was performed.

In 2 fatalities anticoagulant therapy undoubtedly played a part:

The 1st patient died from severe gastrointestinal hæmorrhage complicating an infective diarrhœa: he had refused admission to hospital.

The 2nd patient was a 51-year-old man who had been on anticoagulant treatment for six months when he was admitted with a hæmoglobin of 4 g. per 100 ml. (packed-cell volume 13%). He had had melæna and hæmatemesis for the previous week, yet he had not stopped taking his tablets; and when first seen he was severely shocked (blood-pressure 80/40 mm. Hg, pulse-rate 130 per min.). He was given blood-transfusion and vitamin K, but he died the next day. Necropsy revealed a fresh infarction, presumably precipitated by the severe anæmia. There was no coronary thrombosis. An incidental finding was a small carcinoma of the right kidney with no evidence of metastases.

*Withdrawals*

4 patients had hæmatemeses shown to be caused by peptic ulceration: 1, who presented with severe hæmatemesis, had an inoperable carcinoma of the stomach; in 1 instance a retroperitoneal hæmatoma led to the cessation of treatment; and 1 case was withdrawn from the series because of severe hæmaturia.

1 patient developed such severe skin irritation as to compel cessation of treatment. In 3 anticoagulant therapy was discontinued after mitral valvotomy. Another 2 patients were lost when they moved from the district.

In 5 patients treatment was stopped because of poor intelligence or lack of cooperation, 3 of them having continued their tablets despite hæmaturia.

TABLE III—INCIDENCE OF BLEEDING

| — | No. of patients | Patient-months of treatment | No. of hæmorrhages | No. of hæmorrhages per 100 patient-months | No. of months per patient per hæmorrhage |
|---|---|---|---|---|---|
| Bleeding recorded | 105 | 1776 | 194 | 10·9 | 9·2 |
| No bleeding | 112 | 1496 | 0 | .. | .. |
| Total | 217 | 3272 | 194 | 5·9 | 16·9 |

TABLE IV—BLEEDING EPISODES DURING THE FIRST THREE MONTHS OF LONG-TERM THERAPY

| — | No. of patients | No. of patient-months of treatment | No. of hæmorrhages | No. of hæmorrhages per 100 patient-months | No. of months per patient per hæmorrhage |
|---|---|---|---|---|---|
| Bleeding recorded | 55 | 148 | 62 | 42·0 | 2·4 |
| No bleeding | 162 | 449 | 0 | .. | .. |
| Total | 217 | 597 | 62 | 10·4 | 9·6 |

*Hæmorrhage*

This can be graded in terms of severity: (1) very severe (requiring admission to hospital or causing severe constitutional upset); (2) moderate (persistent hæmaturia for a week or more; or extensive bruising); (3) minor transient occult hæmaturia, or minor bruising).

In this series of 217 cases 105 patients (48·4%) had some hæmorrhagic complication; and together they accounted for 194 bleeding episodes. Of these, 24 were severe, 31 moderate, and 139 mild (table III). Bleeding is especially likely during the first three months of treatment (table IV).

For a more reliable assessment we re-examined patients who were receiving treatment on Dec. 31, 1958. This group included 178 patients who were closely questioned about bleeding episodes during 1958 only. The incidence

TABLE V—INCIDENCE OF BLEEDING IN THE ONE-YEAR GROUP

| — | No. of patients | No. of patient-months of treatment | No. of hæmorrhages | No. of hæmorrhages per 100 patient-months | No. of months per patient per hæmorrhage |
|---|---|---|---|---|---|
| Bleeding recorded | 65 | 573 | 98 | 17·0 | 5·9 |
| No bleeding .. | 113 | 1037 | 0 | .. | .. |
| Total .. .. | 178 | 1610 | 98 | 6·1 | 16·5 |

TABLE VI—BLEEDING EPISODES DURING THE FIRST THREE MONTHS OF TREATMENT IN THE ONE-YEAR GROUP

| — | No. of patients | No. of patient-months of treatment | No. of hæmorrhages | No. of hæmorrhages per 100 patient-months | No. of months per patient per hæmorrhage |
|---|---|---|---|---|---|
| Bleeding recorded | 25 | 67 | 32 | 48 | 2·1 |
| No bleeding .. | 60 | 151 | 0 | .. | .. |
| Total .. .. | 85 | 218 | 32 | 14·7 | 6·8 |

of these episodes during the whole year and during the first three months treatment is shown in tables V and VI.

There is little difference between the whole series and the one-year group. Our figures suggest that 1 patient in 3 will have some sort of hæmorrhagic episode during the first three months of treatment, and that thereafter the likelihood of bleeding is approximately halved.

*Severe bleeding* occurred in 22 patients. There were 2, possibly 3, deaths: the remaining 19 had twenty bleeding episodes which in 9 led to the discontinuation of the drug. Hæmatemesis and melæna accounted for 8 major hæmorrhages, hæmaturia for 7, and epistaxis for 2. 1 patient had extensive bruising, 1 a retroperitoneal hæmatoma, and 1 severe bleeding after dental extraction.

1 patient who had been satisfactorily controlled for eighteen months with phenindione 100–150 mg. daily became "resistant" to the drug. Despite progressive increase in dosage his one-stage clotting-time remained normal until he was admitted with a sudden prolongation of clotting-time and severe generalised bruising and hæmaturia. He was a reliable patient who had been taking his tablets regularly. In this kind of case the thromboplastin-generation test may reveal a coagulation defect in the face of a normal one-stage clotting-time (Hunter and Walker 1954).

Table VII shows that severe bleeding is likely to complicate treatment about once in ten years.

*Moderate bleeding* occurred on 31 occasions in 27 patients: 13 patients had hæmaturia, 9 extensive bruising, and 4 melæna. Hæmoptysis was recorded on 1 occasion;

TABLE VII—INCIDENCE OF SEVERE BLEEDING EPISODES

| — | No. of patients | No. of patient-months of treatment | No. of hæmorrhages | No. of hæmorrhages per 100 patient-months | No. of months per patient per hæmorrhage |
|---|---|---|---|---|---|
| Bleeding recorded | 23 | 352 | 24 | 6·8 | 14·6 |
| No severe bleeds .. | 194 | 2920 | 0 | .. | .. |
| Total .. .. | 217 | 3272 | 24 | 0·7 | 136 |

and spontaneous hæmarthrosis of a knee occurred once, without other evidence of bleeding but with a prolonged prothrombin-time.

*Skin Sensitivity*

3 patients developed skin sensitisation; and in 1 severe pruritus forced us to discontinue the drug. This patient had been treated for two and a half years before any irritation developed.

## The Orthotolidine Test

The orthotolidine (occultest) test is very sensitive to occult hæmaturia (Peyman 1956). 79 of the patients who are regularly using this test recorded 25 episodes of hæmaturia; and in 9 the urine was not macroscopically bloodstained. It is reasonable to suppose that the detection of bleeding at an earlier stage reduces the risk involved; and the test has the additional advantage of distinguishing hæmaturia from the discoloration by phenindione itself.

The detection of occult hæmaturia does not, however, protect the patient entirely from more serious bleeding: often severe macroscopic hæmaturia or even hæmatemesis occurred after a negative test on the previous day. Therefore, although it is worth employing this test as a routine, the patient must be aware of the other complications of anticoagulant therapy. Though the test makes the patient conscious of his disease, this applies, to some extent, to the whole scheme of anticoagulant treatment.

## Conclusions

An unduly prolonged clotting-time may be revealed by an insignificant bruise, but likewise it may herald a fatal cerebral hæmorrhage. Therefore any sign of bleeding tendency, however slight, is serious, and its early recognition is of great importance. For this reason anticoagulant therapy is probably best reserved for intelligent patients; and one must be sure that they understand the instructions given to them.

Unfortunately hæmorrhagic complications seem to be inevitable; but many of the episodes in this series would have been less severe had the patient recognised their importance earlier. In the words of Askey and Cherry (1950), "the successful use of long-term anticoagulant therapy depends on the triad—a vigilant physician, a cooperative patient, and a reliable laboratory".

## Summary

The problems encountered in the management of 217 patients on long-term anticoagulant therapy are discussed.

At an overall average rate of one episode every seventeen months of treatment 48% of patients had complications. Severe hæmorrhages occur about once in 10 patient-years. There were 2 (possibly 3) deaths from treatment.

The routine use of the orthotolidine test for the detection of microscopic hæmaturia is recommended.

I wish to thank Dr. W. G. A. Swan and Dr. Frederick Jackson for their helpful criticism while preparing this paper.

*References overleaf*

## LARYNGEAL SPILL-OVER

T. L. BRADBEER
M.B. Lond., F.R.C.S.
SENIOR EAR, NOSE, AND THROAT REGISTRAR, CHARING CROSS HOSPITAL, LONDON, W.C.2

IN the following case a relatively simple operation cured laryngeal spill-over.

### Case-report

A woman aged 48 had a large right carotid-body tumour excised by Mr. P. F. Philip at Charing Cross Hospital in April, 1957. The tumour arose from the ganglion nodosum of the vagus nerve, and this nerve had to be divided near the base of the skull. Paralysis and sensory loss of the pharynx and vocal cord on the same side were inevitable, but the patient made a good recovery though she was left with a hoarse voice.

Eighteen months later she returned as an outpatient complaining of difficulty in swallowing fluids because of spill-over into the larynx, and of the production of purulent sputum. This had been present, becoming increasingly severe, for four months. A chest radiograph showed a patch of consolidation in the lower lobe of the right lung, and a ' Lipiodol ' swallow showed spill-over, the medium collecting in the right lower lobe. She was thought to have an aspiration pneumonia, and she was therefore admitted to hospital on Nov. 13, 1958. She was treated with a course of tetracycline, breathing exercises, postural drainage, and turning two-hourly.

The clinical signs and radiographic appearance deteriorated. The patch of consolidation enlarged, then further patches appeared higher in the right lung, and by Dec. 4, 1958, a patch had also appeared in the lower lobe of the left lung. She was referred for a laryngological opinion.

When seen by Mr. H. S. Sharp on Dec. 5 she was unable to swallow any fluid without coughing and choking. The cough was bovine, and her voice was only a faint blowing whisper. The right vocal cord was fixed in the paramedian position, and on phonation and coughing the left cord failed to meet it, leaving an opening about 3 mm. wide posteriorly.

Mr. Sharp thought that inability to close the glottis was the main cause of her symptoms, and that some measure to enable closure was needed. A method has been described (Morrison 1948) by which the posterior end of the vocal cord is adducted by moving the arytenoid cartilage to a new position on the cricoid cartilage. For this patient such an operation would have had to be done through a field partly disorganised by removal of the carotid-body tumour, and so instead an attempt to move the anterior end of the cord was made on Dec. 13.

A general anæsthetic was given, and a tracheostomy was performed. The thyroid cartilage was incised vertically about 4 mm. to the right of the midline, and the anterior end of the right vocal cord was mobilised and sewn below the left cord to the inner aspect of the left ala of the thyroid cartilage by two separate catgut sutures which transfixed the cartilage. The wound was closed in layers. The tracheostomy tube was removed forty-eight hours later.

The patient's voice became stronger, and the cough normal. There was no more overflow. Indirect laryngoscopy showed the glottic chink to be shortened, the right arytenoid drawn forward and to the midline, and overlap of the right cord anteriorly by the left one.

A week after operation, sputum culture yielded tubercle bacilli, and treatment with streptomycin and calcium benzamidosalicylate (' Therapas ') was begun. She quickly put on weight, and the chest radiographs showed considerable improvement in the next month. It is impossible to say how much of her improvement was due to restoration of normal closure of the glottis. The preoperative chest radiographs were very suggestive of aspiration effects, with consolidation beginning in the lower lobes. The scarcity of tubercle bacilli in the sputum, and the rapid improvement in the patient's condition, may also support this view.

### Discussion

Overflow into the larynx during swallowing is not uncommon in neurological lesions which cause paralysis or bilateral sensory loss, and in the presence of local neoplasms. In this patient the sensory loss was unilateral and the paralysis largely so. The left vocal cord should have been able to compensate by swinging to the other side, but it could not do this because adduction was limited. This has not been explained.

The standard remedies for laryngeal spill-over are avoidance of fluids in the diet, certain tricks of swallowing (such as tilting the head to one side), tracheostomy, and Morrison's operation for moving a vocal cord which lies too far from the midline. In this case such an operation would have been unusually difficult. As the paralysed cord was not far abducted the simpler anterior approach was used.

This relatively easy procedure might be used in other cases. Postoperative discomfort is very slight, and restoration of movement in the cord is not precluded.

I am grateful to Mr. H. S. Sharp and Mr. P. F. Philip for permission to report this case.

REFERENCE

Morrison, L. F. (1948) *Ann. Otol., &c., St. Louis*, **57**, 945.

DR. FULLER: REFERENCES

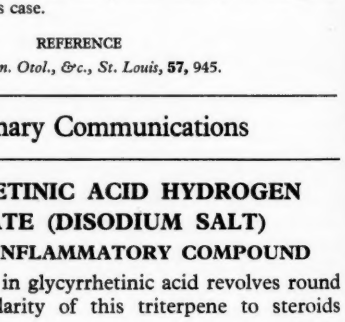
Askey, J. M., Cherry, C. B. (1950) *J. Amer. med. Ass.* **144**, 97.
Bjerkelund, C. J. (1957) *Acta med. scand.* **158**, suppl. 330.
Foley, W. T., McDevitt, E., Symons, C., Wright, I. S. (1955) *Arch. intern. Med.* **95**, 497.
Hunter, R. B., Walker, W. (1954) *Brit. med. J.* ii, 197.
Keyes, J. W., Drake, E. H., Smith, F. J. (1956) *Circulation*, **14**, 254.
Manchester, B. (1957) *Ann. intern. Med.* **47**, 1202.
McDevitt, E., Carter, S. A., Gatje, B. W., Foley, W. T., Wright, I. S. (1958) *J. Amer. med. Ass.* **166**, 592.
Medical Research Council (1959) *Brit. med. J.* i, 803.
Nichol, E. S., Borg, J. F. (1950) *Circulation*, **1**, 1097
Peyman, M. A. (1956) *Lancet*, ii, 496.
Suzman, M. M., Ruskin, H. A., Goldberg, B. (1955) *Circulation*, **12**, 338.
Tulloch, J., Wright, I. S. (1954) *ibid.* **9**, 823.
Waaler, B. A. (1957) *Acta med. scand.* **157**, 289.

# Preliminary Communications

## GLYCYRRHETINIC ACID HYDROGEN SUCCINATE (DISODIUM SALT)

### A NEW ANTI-INFLAMMATORY COMPOUND

CURRENT interest in glycyrrhetinic acid revolves round the structural similarity of this triterpene to steroids (see figure), and the possible therapeutic application of some of the corticosteroid-like properties [1] of this non-steroid drug. Three recent articles have drawn attention to the use of glycyrrhetinic acid in the treatment of inflammatory conditions.[2–4] The suggestion has been made that fully controlled clinical trials should be carried out, and one such trial has in fact been reported.[5] We report here our first results with a derivative of this compound.




The low solubility of the parent glycyrrhetinic acid in

1. Finney, R. S. H., Somers, G. F., Wilkinson, J. H. *J. Pharm. Lond.* 1958, **10**, 687.
2. *Practitioner*, 1959, **182**, 273.
3. *Pharmaceutical Journal and Pharmacist*, 1959, **128**, 75.
4. *British Medical Journal*, 1959, i, 914.
5. Colin-Jones, E. *ibid.* p. 1413.

body fluids precludes its systemic administration in man and has considerably restricted its usefulness. At the suggestion of Dr. S. Gottfried (Biorex Laboratories Ltd.) two of us (E. E. T. and, in part, D. E. M. W.) have for some time been studying the synthesis of water-soluble derivatives. An early member of the series seemed promising on the results of screening tests for anti-inflammatory activity and has been investigated further. This is the disodium salt of glycyrrhetinic acid hydrogen succinate (G.A.H.S.) which is freely soluble in water, forming a stable solution (pH 7·7) which can be sterilised by filtration.

Some of the anti-inflammatory and pharmacological properties of G.A.H.S. have been studied.[6] The anti-inflammatory activity in rats is $^1/_5$th that of hydrocortisone hemisuccinate by the cotton-pellet method.[7] Intravenous doses up to 23 mg. per kg. body-weight given to anæsthetised cats have no significant effect on the blood-pressure, heart-rate, respiration, or autonomic nervous system. G.A.H.S. taken by mouth appears in the blood after one to two hours and is then rapidly eliminated. The metabolism of the compound, however, still requires elucidation.

The acute toxicity of the drug has been studied in mice, rabbits, and cats, while its chronic toxicity has been determined in rats and cats.

Single intravenous doses of 16 mg. per kg. given to rabbits and 23 mg. per kg. given to cats had no untoward effect. Mice tolerate single doses as high as 250 mg. per kg. by mouth and by subcutaneous injection; the $LD_{50}$ is 101 mg. per kg. by the intraperitoneal route and 43 mg. per kg. by intravenous injection. Rats given 25 mg. per kg. intraperitoneally twice weekly for sixteen weeks exhibit some sodium and water retention, an effect not seen in cats. Serum-transaminase levels were determined in a pilot experiment in which a rabbit was given 2 mg. G.A.H.S. per kg. intraperitoneally for sixteen days. There was no liver-cell damage demonstrable by these tests: the serum glutamic-oxaloacetic transaminase was 13–18 units, while glutamic-pyruvic transaminase remained unchanged at 10 Karmen units per ml. (J. H. Wilkinson, personal communication to A. L. T.). The blood-glucose levels of rabbits show no definite changes when 20 mg. G.A.H.S. is given intravenously to fasting animals or injected ten minutes before a glucose-tolerance test.

No spasmolytic effect of G.A.H.S. has been observed, but it has a very slight atropine and anti-histamine action. When injected intradermally into sensitised guineapigs in doses ranging from 1·25 to 5·0 mg., G.A.H.S. has an inhibitory action against Arthus reactions provoked by simultaneous injections of antigen (1–11·65 mg.). (Egg albumin is used as the antigen in these experiments.)

Preliminary in-vitro tests using human blood (whole blood and washed red cells) showed no hæmolytic effect at blood-levels up to 0·5 mg. G.A.H.S. per ml., well above expected concentrations in man. This finding is of interest in view of the possible relation of glycyrrhetinic acid to the triterpenoid sapogenins.

Further studies on G.A.H.S. are in progress, mainly with reference to its anti-inflammatory action in experimental tuberculosis and its effect on immunity. Pharmacological studies on the antiallergic and antiasthmatic effects of this compound are also being made. A pilot trial in ulcerative colitis giving 250 mg. G.A.H.S. in 120 ml. enemata has given encouraging results. Here the action of the drug is local, and there is probably no absorption. Further trials in ulcerative colitis and in the treatment of gastric and duodenal ulcer are planned. Clinical trials are also in progress in the dental, gynæcological, dermatological, and rheumatological fields; the biochemical control of these trials is mainly concerned with the study of the electrolyte balance and steroid excretion.


Derby Chest Clinic — H. M. BROWN, M.D. Edin., M.R.C.P.E.

Department of Physical Medicine, St. Thomas's Hospital, London, S.E.1 — B. G. B. CHRISTIE, M.B. Lond., M.R.C.P., D.PHYS.MED.

Department of Dermatology, Brighton, Tunbridge Wells and Chichester Group Hospitals — E. COLIN-JONES, M.B. Lond., F.P.S.

Department of Biology, College of Technology, Leicester — R. S. H. FINNEY, M.SC. Manc., B.SC. Lond.

Institute of Obstetrics and Gynæcology, Postgraduate Medical School of London — W. G. MACGREGOR, F.R.C.S., M.R.C.O.G.

Birmingham Chest Clinic — J. MORRISON SMITH, M.B. Glasg., M.R.C.P.E., D.P.H., D.T.M. & H., T.D.D.

Department of Pharmacy, Sunderland Technical College — W. G. SMITH, PH.D. Lond., F.P.S.

Department of Pharmacology, Guy's Hospital Medical School, London, S.E.1 — F. M. SULLIVAN, B.SC. Edin.

Department of Pathology, Royal Berkshire Hospital, Reading — A. L. TÁRNOKY, PH.D. Lond., F.R.I.C.

Department of Chemistry, Bedford College, University of London — E. E. TURNER, M.A. Cantab., D.SC. Lond., F.R.I.C., F.R.S.

D. E. M. WOTTON, B.SC. Lond.

Department of Medicine, The General Infirmary, Leeds, 1 — G. WATKINSON, M.D. Lond., M.R.C.P.


## TROPICAL EOSINOPHILIA
### EXPERIMENTS WITH TOXOCARA CANIS

RECENT investigations by a number of workers indicate that asthma with eosinophilia,[1] tropical eosinophilia,[2] or eosinophil lung [3] may be due to invasion by the larvæ of certain nematodes for which man is not the natural host.[4–11] Hence the following experimental observations seem worth reporting:

24 guineapigs with eosinophil-counts of up to 3% were each given intragastrically 1 ml. of a suspension of 1000–1400 embryonated eggs of *Toxocara canis*. Within a week or two they all showed a considerable increase of eosinophils in the blood, a maximum of 30–55% being reached in the third week. Thereafter the count came down to 10–20% about the sixth week. 3 of the 4 animals that were X-rayed showed definite mottling in the lung fields with lobar atelectasis in 1. The 3 animals which were killed had scattered reddish patches on the lungs and whitish granules on the liver. Histological section showed peribronchial accumulation of eosinophils, and eosinophilic exudate in the bronchioles and alveoli, along with diffuse interalveolar infiltration by eosinophils. Segments of larvæ were also found. The liver sections showed numerous granulomatous areas, often with remnants of larvæ in the centre and eosinophils in profusion at the periphery.

Another series of 24 guineapigs were given in similar manner repeated feeds of 450–500 embryonated eggs of

6. Finney, R. S. H., Tárnoky, A. L. British Pharmacological Society, London meeting, 1959.
7. Meier, R., Schuler, W., Desaulles, P. *Experientia*, 1950, 6, 469.


1. Roy, B. C., Bose, C. C. *Calcutta med. J.* 1918, **12**, 268.
2. Weingarten, R. J. *Lancet*, 1943, i, 103.
3. Chaudhuri, R. N. *Indian med. Gaz.* 1943, **78**, 575.
4. Beaver, P. C., Snyder, C. H., Carrers, G. M., Dent, F. H., Lafferty, F. W. *Pediatrics*, 1952, **9**, 7.
5. Chaudhuri, R. N. Report of Scientific Advisory Board, Indian Council of Medical Research, New Delhi, 1956; p. 15.
6. Chaudhuri, R. N. *J. Indian med. Ass.* 1956, **27**, 195.
7. Editorial. *ibid.* p. 210.
8. Danaraj, T. J., Da Silva, L. S., Schacher, J. F. *Proc. Alumni Ass. Malaya*, 1957, **9**, 172.
9. Gault, E. W., Webb, J. K. G. *Lancet*, 1957, ii, 471.
10. Buckley, J. J. C. *Trans. R. Soc. trop. Med. Hyg.* 1958, **52**, 335.
11. Saha, T. K., Bandyopadhyay, A., Chaudhuri, R. N. *Bull. Calcutta School trop. Med.* 1959, **7**, 99.

*Toxocara canis* daily for fourteen days. All showed similar hypereosinophilia (up to 51%) which lasted longer—eight weeks or more. Incidentally, 5 of them showed respiratory distress. Of 3 animals X-rayed twice, 2 showed lung changes. 2 died and a few were killed, with similar necropsy findings.

On March 14, 1959, a volunteer was given by mouth about 100 embryonated eggs of *Toxocara canis* suspended in normal saline. His blood-count at the time was: 6700 per c.mm. (neutrophils 57%, lymphocytes 37%, monocytes 1%, eosinophils 5%), the absolute eosinophil-count being 335 per c.mm.

The eosinophilic response was striking. On the thirteenth day after the feed the eosinophils increased to 26% (2704 per c.mm.). On the thirtieth day the white-cell count was 21,800 with 62% eosinophils (13,516 per c.mm.). Thereafter the eosinophilic level remained between 40 and 50% with an absolute count varying from 5000 to 8000 per c.mm. A count on July 27, four and a half months after the ingestion of eggs, showed 12,800 white cells per c.mm. (neutrophils 24%, lymphocytes 27%, monocyte 1%, eosinophils 48%). Lately he has developed an irritant cough worse at night. This symptom and persistent massive eosinophilia simulate tropical eosinophilia.

Our thanks are due to Mr. P. Ghose for technical assistance.

R. N. CHAUDHURI
M.B., F.R.C.P.E.
Professor of Tropical Medicine

T. K. SAHA
M.B.
Assistant Research Officer

Clinical Research Unit
(Indian Council of Medical Research),
Calcutta School of Tropical Medicine,
India

# Medical Societies

## SOCIETY FOR SOCIAL MEDICINE

THE third annual meeting of the society was held in Dundee on Sept. 17–19, and some of the communications are briefly summarised below.

### Industry

Prof. ALEX MAIR (Dundee) reported an investigation into dust hazards of jute manufacture, which is the major industry of Dundee. Although it had long been a clinical impression in hospital practice in Dundee that workers in the jute industry were more likely to have chronic respiratory disease, no specific dust disease comparable with byssinosis in cotton workers had ever been described. Comparisons of workers in jute, flax, and non-textile trades in Dundee by means of a symptom questionnaire failed to demonstrate any excess of chronic respiratory disease in jute workers but disclosed a previously unsuspected prevalence of byssinosis in flax workers. Workers whose questionnaires revealed chronic respiratory symptoms were further examined, and the finding of a byssinosis-like disease was confirmed by clinical examination and by ventilatory studies.

Dr. R. S. F. SCHILLING (London) described the conduct of an epidemiological study of cotton factories with a view to identifying the specific factor producing byssinosis. By correlating the prevalence of pulmonary symptoms with indices of cotton-dust density and particle size, he was led to the view that symptoms were largely produced by medium-size particles.

Dr. C. B. MCKERROW (Pneumoconiosis Research Unit) described the results of experiments designed to examine the proposition that a specific allergy was concerned in byssinosis. He and Dr. J. C. Gilson had measured the indirect maximum breathing capacity and airways resistance of card-room workers and had shown that ventilatory capacity falls and airways resistance rises during the working day. Since no such changes occurred in the same subjects when removed from the card-room, or in other subjects exposed to large quantities of inert dusts, it is assumed that cotton dust contains an active substance with specific effects on ventilatory function. The exposure to a cotton card-room of normal subjects who had never previously encountered cotton dust demonstrated a striking effect on their ventilatory function. Two-thirds of these subjects had acute impairment of ventilatory capacity after one morning's exposure. It was concluded from this that allergy is unlikely to provide an explanation of the effects of cotton dust.

Experiments with mill workers exposed to concentrations of varying particle size showed that a suspension of fine particles of cotton dust produced as much effect as unfiltered air from the card-rooms, and suggested that the fine particles were important in producing changes in ventilatory function.

Other experimental work showed that cotton contained a substance capable of producing ventilatory changes at all stages of its manufacture whereas jute and sisal were inert, at least at the milling stage. It is concluded that either the substance is totally absent from jute and sisal or that differences in the processing techniques result in its elimination from these materials.

Discussion which followed the presentation of these papers centred largely on the difference between the epidemiological and physiological evidence relating to the importance of particle size. Dr. Schilling thought that the discrepancy was probably resolved by noting that medium-size particles were incriminated as concerned with the production of symptoms, and that this was not invalidated by the demonstration that fine particles produce ventilatory changes.

Dr. C. R. LOWE (Birmingham) presented data on absenteeism and works injuries in relation to smoking habits. The mean number of works injuries declined with age but increased according to amount smoked when the influence of the association of age with smoking habits was eliminated by standardisation. The mean number of days lost for medical reasons increased with age and it increased with amount smoked (age standardised). Absences for reasons other than sickness showed no association with either age or amount smoked. The relation between amount smoked and the incidence of works injury was most apparent in the younger men, whereas the relation between amount smoked and medical absence was most evident for the older men. Dr. Lowe discussed this evidence against the background of current controversies concerning the pathological significance of cigarette smoking. A substance so heterogeneous as tobacco smoke might well contain several different pathogenic principles. The finding of an association between smoking and medical absence in older men was not surprising in view of the importance of respiratory disease as a cause of sickness absence in Birmingham. In considering the association of smoking with works injury among the younger men the possibility of a third factor predisposing both to a taste for smoking and to likelihood of injury might be borne in mind. Such a third factor might be very unlikely as an explanation for the association between smoking and lung cancer but quite likely in the present context.

### Child Health

Dr. E. G. KNOX (Newcastle) referred to the common clinical impression that certain uncommon diseases tend to " come in threes ". A consideration of this belief leads to consideration of the frequency density of lengths of intervals between randomly occurring events. The distribution is exponential, and as interval lengths get shorter their frequencies increase. This inevitably leads to the recording of rare events in clusters

and makes distinguishing between clusters that are merely random, and clusters which are biologically significant, a difficult process. Dr. Knox examined data on congenital œsophageal atresia in the light of these comments. Data from Birmingham and from Newcastle show evidence of clustering. Annual totals in both areas were non-random but elimination of the effects of a linear trend of increasing diagnosis failed to eliminate all non-randomness. There is no evidence of consistent seasonal variation in incidence. Analysis of the data was presented in another way by comparing the observed and expected numbers of cases in weeks following the recording of a case. The method reveals an excess of observed over expected in the early weeks after a case is reported. This method, however, is not susceptible to significance testing.

Dr. Knox concluded that the impression of clustering in the reporting of cases is of biological importance and not merely a random phenomenon but stressed the need for suitable statistical means of determining significant non-randomness in similar studies.

Dr. JOSEFINE WEBB (Oxford) had examined the incidence of infections and of antibiotic and sulphonamide treatment in three groups of children: those with lymphatic leukæmia, those with other forms of leukæmia, and those with malignant disease other than leukæmia. No significant difference between the groups was found when the infectious diseases were considered in aggregate except for a slight tendency for leukæmia patients to have had more infections in the year preceding onset. Pneumonia, however, showed a higher incidence and shorter intervals before onset in the leukæmia groups. No difference was found between lymphatic and other leukæmias. The incidence of treatment with antibiotics, however, was significantly higher at all intervals before onset in the non-lymphatic leukæmia group than in the other groups and the incidence of treatment with sulphonamides was higher in the lymphatic leukæmia group in the eighteen months prior to onset of the leukæmia.

Dr. MERVYN SUSSER (Manchester) introduced the results of an investigation which he conducted with Dr. Zena Stein into the mode of operation of social selection in the ascertainment of educationally subnormal children. The family background of such children was classified according to criteria which were believed to distinguish valid cultural categories. The main groups were characterisable colloquially as "respectable" and "rough". In the "respectable" group all children showed severe neurological lesions or had I.Q.s at imbecile level. None of the ascertained children with high-grade intelligence were in this category. The likely explanation of this finding is that social and cultural selection plays a part in determining the ascertainment of educationally subnormal children. This consideration may seriously invalidate some studies of mental subnormality where ascertainment of dull children is assumed to be highly correlated with I.Q.

Mrs. MARGOT JEFFERYS (London) presented the results of a study of polio-vaccine uptake in a London out-county housing estate. Analysis showed that 75% of the five-year olds, 66% of the eight-year-olds, and 45% of the fourteen-year-olds had been vaccinated against poliomyelitis. The vaccinated groups had a higher rate of uptake of immunisation against diphtheria and smallpox than the unvaccinated. Little relationship was detectable between uptake of vaccine and social class. Size of family was however correlated with vaccine uptake; the smaller families being more heavily represented among the vaccinated group. Children with mothers who worked outside the home were more heavily represented among the vaccinated group, but this is largely to be accounted for by the finding that these children came from the smaller families.

## Hospital Patients

Dr. JEAN MACKINTOSH and Dr. F. N. GARRATT (Birmingham) gave the results of part of an inquiry into general hospital admissions in the Birmingham area and an attempt to assess the number of "avoidable" admissions. Admissions were scrutinised by a hospital consultant and were regarded as unavoidable if the patient needed facilities most readily provided in hospital, such as surgical treatment, special investigations, and special nursing. Comparison with a similar study reported by an experienced general practitioner showed that opinion differed sharply as to what constituted avoidable admission, the general practitioner classifying a much larger proportion as avoidable.

Dr. R. SUTHERLAND (Leeds) discussed the problem of whether delay in seeking treatment for breast cancer materially affects prognosis. Material assembled from the literature shows that if survival is examined according to length of interval between onset of symptoms and operation a high survival-rate for short-delay patients is followed by a poor survival-rate for intermediate periods of delay. As delay increases beyond about twelve months, however, the survival-rate improves and reaches a much more favourable level than in short-delay patients. Dr. Sutherland's interpretation of these findings is that short-delay patients represent an unselected group with respect to tumour malignancy whereas the intermediate delay patients include an increasing proportion of patients where rapid growth of the tumour precipitates consultation. The long-delay group necessarily includes a large proportion of patients with tumours of low malignancy. The view may be taken that since the short-delay patients who are presumably representative have better survival-rates than all patients, early operation improves the chances of survival.

Dr. R. WEIR (Aberdeen) presented data on patients admitted to two hospitals for perforation of duodenal ulcers. The proportion of males to females was of the order of nine males to one female. There had been a secular rise in the number from a low level in 1946 to a peak in 1954 since when there has been a fall almost to the 1946 level. The maximum incidence in males rises to a peak between ages 45 to 65 years. There was a significant excess of single men in the age-group 40 to 50 years. The social-class distribution shows that the maximum incidence of perforated duodenal ulcer is in class V and that there is a steady trend to a low incidence in class I.

## Serum-proteins and Stout

Dr. R. M. ACHESON and Prof. W. J. JESSOP (Dublin) had studied serum-protein levels in a number of men retired from work in a large brewery in Dublin. Gamma-globulin levels showed an association with age, increasing from 65 years to 80 years and thereafter falling. Albumin levels were slightly but significantly higher in those who took meat twice a day than in those who took it less than twice. Men who drank more than twelve pints of stout per day showed a raised beta-globulin. Smaller quantities of stout produced no difference from teetotallers. No association between serum-albumin levels and proteinuria was found, although the gamma-globulin level was raised in the proteinuric group.

## Occupation and Age

Dr. LILLI STEIN presented reasons for believing the present tabulation by the Registrar General of occupation according to age to be inadequate for many purposes and misleading. At present the only published tables are for occupied and retired men together for England and Wales and for the ten regions grouped in five "social classes". For smaller regional units the tables give the distribution for all men aged over 15 years occupied and retired. However, important variations exist in the proportions of retired, and in the age-distribution of the social classes in different regions. Variations in the class distribution at different ages occur, and the net result of these variations is to render impermissible assumptions that age-distributions are comparable within social classes in different regions. A classification which was to be generally meaningful would require some ten classes each of reasonable size and in which status and type of occupation would be differentiated. Tabulation should include age by occupational class and marital status and should distinguish between occupied and retired men as well as women and preferably should show smaller regional divisions than at present.

# Reviews of Books

## A Short History of Psychiatry

ERWIN H. ACKERKNECHT, professor of the history of medicine, University of Zurich. Translated by SULAMMITH WOLFF, M.A., M.R.C.P., D.P.M. New York and London: Hafner Publishing Co. 1959. Pp. 98. 25*s*.

IN this small, admirable, and well-translated volume Professor Ackerknecht surveys the origins of present-day psychiatry. For brevity, he has omitted interesting though less relevant material from Egypt, Mesopotamia, China, and the Arabs, for example. Unfortunately for English readers he does not say much about developments and teaching in this country, although the excellent work of Kathleen Jones [1] makes much of this deficiency good. His handling of early German psychiatry is deservedly rich and he usually resists the temptation to recite lists of unpronounceable names meaningless to almost all readers and undocumented in the text. The psychoanalytical school is placed firmly but kindly in historical perspective and is not seen as the climax and fulfilment suggested in the standard work of Zilboorg.[2] This book can be recommended as the most balanced and readable work on its fascinating subject so far written, and should be obligatory reading for any kind of D.P.M. There still remains a place, however, for a much larger definitive work of reference: there are perhaps three scholars in the world capable of writing this, and we hope that one of them will one day do so.

## Social Work in Tuberculosis

MARGARET COLTART, M.A., A.M.I.A., head almoner, Brompton Hospital, London; HELEN RAINE, B.A., tuberculosis welfare officer, Middlesex County Council; ELIZABETH HARRISON. London: Chest and Heart Association. 1959. Pp. 144. 12*s*. 6*d*.

THE large, widely scattered band of tuberculosis-dispensary almoners were among the earliest specialised groups of paramedical physicians' mates. They became very skilled at providing sympathy, support, guidance, rent, clothing, a job, a home, meals, money, and the host of other essentials in the "social medicine" required by a disabled patient and his family. A steady reduction in the incidence and severity of tuberculosis and its sequelæ has lately led chest physicians and their health visitors and almoners to a closer interest in other conditions. The new endeavour is directed towards making available to bronchitics, asthmatics, and emphysematous and lung-cancer patients, medical and welfare facilities similar to those which have been successfully provided for the tuberculous attending hospital and chest clinics. There is as yet in this country no book to guide the less experienced chest-department social worker through the maze of welfare resources—Governmental and voluntary—available for all her patients. In this widening sphere, the young chest-clinic almoner needs to develop a clear insight into her place and techniques in helping each type of chronic chest patient to accept and cope with the limitation of activity and earning capacity which almost inevitably follows the diagnosis.

For the chest-hospital and the chest-clinic almoner who still finds most of her efforts directed towards the problems of tuberculous patients, this book ably summarises the background and principles of social care. Examples of many case-histories are excellently set out and form the best part of the book. In the full but less sparkling account of available services, unnecessarily complicated sentences sometimes make heavy reading. Voluntary tuberculosis care committees surely deserve more than the 15 lines devoted to their constitution, purpose, and activities. There are 30 pages devoted to purely historical detail of tuberculosis almoning in bygone days, and they could profitably have been replaced by guidance on special social needs and their fulfilment for chest cases other than the tuberculous.

This is a good little book for many beside the "social work students and others in the same field" for whom it is primarily intended.

1. Jones, K. Lunacy, Law and Conscience, 1744–1845. London, 1954.
2. Zilboorg, G. History of Medical Psychology. New York, 1941.

## Surgery of the Ear

GEORGE E. SHAMBAUGH, Jr., M.D., professor of otolaryngology, Northwestern University Medical School. Philadelphia and London: W. B. Saunders. 1959. Pp. 669. 152*s*. 6*d*.

IT is a sign of the times that less than a quarter of this textbook of otology is devoted to the treatment of sepsis in the middle ear. Dr. Shambaugh's work gives a balanced picture of aural surgery today, and skilfully combines theory with practical applications. The surgery of deafness has progressed greatly in recent years, and this subject provides the high spot of the book. The chapter on malignant disease of the ear is rather disappointing. Admittedly the outlook is poor in the majority of cases, yet the use of an accurately dosed supervoltage beam after radical surgery, as practised in the United Kingdom, is likely to produce better results than radium needles, which are recommended in the book. The text has been written with great care, and it is therefore surprising to find "Bell's palsy" repeatedly used to describe traumatic and other forms of facial paralysis. The volume will be read with pleasure and profit both by the student and by the master of otology.

## Skin Diseases in the African

G. H. V. CLARKE, M.A. Cantab., M.B. Lond., A.R.I.C., senior specialist (dermatology), H.M. Overseas Medical Service, Federation of Nigeria. London: H. K. Lewis. 1959. Pp. 169. 84*s*.

THIS book is really an atlas of skin diseases of Africans with a strong bias towards Nigerians, and within the limits imposed by this form the material has been well selected and arranged. Diseases are grouped according to their frequency in Africans as compared with Europeans, and most attention is given to those found almost exclusively in the former. Leprosy and yaws, having been fully dealt with in other publications, are not here covered exhaustively. In an introduction, the proportions of cases of different types attending dermatological clinics in Lagos are given; and it is interesting to note the relative rarity of acne vulgaris, alopecia, warts, lupus, psoriasis, rosacea, and tropical ulcer and the surprising frequency of prickly heat. The descriptions accompanying the numerous illustrations are brief; most pages in the book consist of 2-4 photographs in black and white and a few lines of print. Such brevity is probably the only alternative to a comprehensive discussion of the peculiar forms skin diseases take in Africans, but the reader may be misled by the title into expecting more than a briefly annotated atlas. In the preface, the author states that the photographs are "of varying quality" and this unfortunately is so true that some are of no value. One of the most valuable parts is the full bibliography, which covers 48 pages. The book is intended primarily for practitioners new to Africa, but the hope is expressed that the bibliography will prove useful also to those with more experience. These intentions may be fulfilled, and thereby a useful service will have been performed.

## Survey Methods in Social Investigation

C. A. MOSER, reader in social statistics, University of London. London: William Heinemann. 1958. Pp. 352. 35*s*.

THIS text may not have a wide medical audience, but, for those who have to conduct or interpret social surveys relating to medicine, Dr. Moser's book should prove invaluable. Based on a series of lectures on survey methods, it gives a clear and simple account of the development of the techniques involved and a detailed exposition of the practical steps leading from planning to recording and analysis. The main emphasis lies on sampling procedures, and the principles and practice of sampling and the calculation of standard errors are set out without too much statistical detail. Interviewing is given the prominence usual in sociological texts; and there is much in sociological experience that can be applied to history-taking in clinical research. The problem of response or lack of it in social survey is discussed in the sensible, practical, and clear manner which makes this book an essential reference for any serious worker in epidemiology or social medicine.

THE LANCET
LONDON 3 OCTOBER 1959

## Œsophageal Cancer

THERE can be no denying the misery of a man with cancer of the gullet: nor our inability to cure him. Palliation has not proved easy. In the era between the wars attention was riveted on preventing starvation rather than on relieving obstruction. Thus the order of the day was gastrostomy, which might prolong life a little but which also prolonged misery by obstruction—a misery to which the patient's inability to swallow saliva contributed considerably. Today, in awareness that gastrostomy produced quite the reverse of palliation, thoughts have returned to the use of indwelling tubes. GOUREVITCH [1] has described in these columns his modification of the Symonds and Souttar tubes for lesions low in the gullet or at the cardia itself, and his method of introducing it. In the six cases he recorded, the patients survived for only a short time (this method is reserved for cases found to be inoperable by other means); but swallowing appeared to remain satisfactory until death. HEIMLICH et al.[2] have used plastic tubes of rather similar design for insertion through high lesions: like GOUREVITCH they rely on an approach to the lumen close to the growth rather than via the oropharynx through an œsophagoscope, though their attack is proximal through a cervical incision, to avoid a thoracotomy incision, while for the lower lesion it is distal through the stomach. WEISEL et al.[3] have used the more usual method of insertion after dilatation under endoscopic vision. They have presented the results in 103 consecutive cases (82 men, 21 women) seen between 1948 and 1957 and subjected to intubation because of either the extent of the lesion or metastasisation in all but 11, who had some secondary disorder severe enough to preclude operation. The series is remarkable in that there were no deaths due to intubation: there can be few who have not encountered cases of fatal mediastinitis as a result either of splitting the growth at dilatation or misdirecting the tube through a necrotic lesion. WEISEL and his colleagues diagnosed mediastinitis in 16 patients, who suffered nothing worse than a raised temperature—not even a mediastinal abscess. Perhaps the secret of their success lay in their postoperative care—a routine X-ray check using either barium or 'Lipiodol' after three days' absolute starvation. Moreover (though this is not directly stated) apparently tubes did not subsequently pass down the gut, though dislodgement upwards occurred in 1 case. Perhaps polyethylene was a good choice of material for the tube; certainly these workers believe that the œsophagus and mediastinum tolerate synthetic plastics better than rubber or metal, which may presumably tend to promote ulceration of the growth and thus disimpaction of the retaining flange of a tube. Survival-times ranged from 3 weeks to $2^1/_2$ years with a mean of $8^1/_2$ months. Simple intubation proved more satisfactory than palliation by by-pass operations or resection and bridging the gap with plastics on the basis of BERMAN's experiments.[4]

The importance of palliative procedures is emphasised by a report from the Mayo Clinic on the treatment of 909 cases seen there between 1946 and 1956 [5]; only 22·7% of patients could be submitted to resection, and in the majority of these the lesion was at the cardia. Only 3·9% survived five years—a dismal figure which is nevertheless probably better than most. In a sizeable personal series of 336 cases treated over much the same period COLLIS [6] achieved resection in 44%—again mostly with lesions at the lower end, those at the upper end in particular being submitted to irradiation therapy with or without intubation. (COLLIS' and the Mayo Clinic series may not be strictly comparable since COLLIS' 336 patients were all admitted to hospital while the 909 were "encountered at the Mayo Clinic" and so may include those seen only as outpatients.) In a smaller series MACMANUS and his colleagues,[7] while achieving a 55% resection-rate in 115 patients admitted between 1947 and 1953, found a five-year survival of only just over 4% (5 cases). As far as can be ascertained from SWEET's [8] figures only 4% of his patients with midthoracic growths survived five years, and there is some uncertainty as to whether this refers to patients admitted or to those who succeeded in leaving hospital; but he does make the point that where resection was considered to have been undertaken with good hope of cure (31 out of 182 operations) 14% of those with midthoracic growths who left hospital survived five years, as did 34% of those with lower œsophageal growths (compared with 17% of all operated on for growths in this area). Such figures, though surrounded by ifs and buts, may indicate a direction for the optimistic surgeon who responds to a glimmer of hope, particularly if cytology [9] can sometimes present the diagnosis earlier than older methods of investigation. Unfortunately GEPHART and GRAHAM [10] found this method less accurate for lesions of the cardia than of the œsophagus proper: and it is the lesions at the cardia that may occasionally escape confirmation by radiology and endoscopy after symptoms have sounded the alarm, and where surgery can offer most hope—small though that hope still is.

1. Gourevitch, A. *Lancet*, Sept. 5, 1959, p. 258.
2. Heimlich, H. J., Greenlees, T. W., Winfield, J. M. *J. Amer. med. Ass.* 1956, **161**, 192.
3. Weisel, W., Raine, F., Watson, R. R., Frederick, J. J. *Ann. Surg.* 1959, **149**, 207.
4. Berman, E. F. *ibid.* 1952, **135**, 337.
5. Ellis, F. H., Jackson, R. C., Krueger, J. T., Moersch, H. J., Clagett, O. T., Gage, R. P. *New Engl. J. Med.* 1959, **260**, 351.
6. Collis, J. L. *Lancet*, 1957, ii, 613.
7. Macmanus, J. E., Paine, J. R., Dunn, J., Merdinger, W. *Surgery*, 1956, **40**, 510.
8. Sweet, R. H. *J. Amer. med. Ass.* 1954, **155**, 422.
9. Raskin, H. F., Kirsner, J. B., Palmer, W. L. *J. Amer. med. Ass.* 1959, **169**, 789.
10. Gephart, T., Graham, R. M. *Surg. Gynec. Obstet.* 1959, **108**, 75.

## Bronchiectasis in Childhood

OBSTRUCTION of a major bronchus may lead to bronchial dilatation by damming back secretions distal to the block, and in primary tuberculosis glandular enlargement often produces bronchiectasis in this way.[1–3] Obstruction of peripheral bronchi resulting in significant absorption collapse of lung also gives rise to bronchiectasis; for the bronchi in the collapsed lung, being in communication with the atmosphere, dilate to compensate for the shrinkage in lung volume.[4 5] If the collapsed lung re-expands, the associated bronchiectasis will disappear provided that supervening infection has not seriously damaged the bronchial walls [4–7]; and LEES [8] has shown that reversible bronchiectasis of this type is comparatively common in diseases such as pertussis where viscid secretions are abundant. Some have long maintained that bronchiectasis may arise in yet another way—from mere weakening of the bronchial walls by infective processes without abnormal mechanical dilating stresses [9–13]—but this view has been generally accepted only since widespread use of bronchography has revealed how commonly bronchiectasis arises in cases of pulmonary tuberculosis where there is neither significant pulmonary collapse nor obstruction of major bronchi. Now WILLIAMS and O'REILLY [14] have confirmed that non-tuberculous bronchopulmonary infection may also alone give rise to bronchiectasis, and they report that the associated clinical pattern differs from that of bronchiectasis in which the primary ætiological factor is absorption collapse.

They studied 241 cases of bronchiectasis from the inception of the disease; and after setting aside cases associated with fibrocystic disease of the pancreas, primary pulmonary tuberculosis, congenital malformation of the bronchi, and miscellaneous lung infections, they were left with two groups of cases: one a group of 37 in which the initial disease was subacute pyogenic pulmonary collapse, and the other a group of 57 in which the initial disorder was a non-specific bronchiolitis sometimes accompanied by interstitial pneumonia. In the collapse group the onset of the disease was acute and occurred most commonly between the ages of 2 and 6 years; pyogenic organisms were usually recovered from the sputum in the early stages of the illness; there was no evidence of chronic upper-respiratory infection or of wax keratosis; the bronchiectasis affected mainly the proximal bronchi, was localised, often reversible, and did not progress; and symptoms tended to clear up a year or two after the onset. In the bronchiolitis group, on the other hand, the onset of the disease was usually insidious and seldom occurred after the age of 3 years; pyogenic organisms were rarely recovered from the sputum in the early stages; chronic upper-respiratory infection was present in all, and wax keratosis in two-thirds, of the cases; the bronchiectasis affected mainly the peripheral bronchi, was sometimes generalised, was never reversible, and occasionally spread; and symptoms were persistent although tending to abate between the ages of 10 and 14 years. Perhaps the most striking feature which emerged from the investigation was the apparent difference in the role of hereditary factors in the ætiology of the disease in the two groups: in the collapse cases there was no family history of chronic respiratory disease, whereas in the bronchiolitis cases there was a family history of proven bronchiectasis in 14% and a family history of chronic respiratory disease in 38%. Not unexpectedly, surgical treatment proved more effective in collapse cases than in bronchiolitis cases with their greater liability to generalised disease, and WILLIAMS and O'REILLY suggest that in the latter group operative intervention should be confined to removal of destroyed lobes, and that even this should be deferred until the second decade.

These workers believe that the two types of disease they describe are distinct clinical entities—a conclusion that seems to be well justified by their findings. Their study also shows once again the need for prolonged observation before embarking on surgical treatment of bronchiectasis.[15]

## Scoliosis

DURING the past thirty years the prevention and treatment of most deformities have been greatly improved. There remains, however, a hard core of severe deformities which are still ill-understood and either cannot be prevented or are refractory to treatment. Foremost among these are certain severe deformities of the spine, and notably scoliosis. Scoliosis implies both a lateral curvature and a complex rotational deformity of the spine with associated deformities of the thoracic cage and secondary deformities of the lungs, heart, and great vessels. Not only is this disability unsightly and difficult to disguise but also it has permanent ill effects on the patient's health and particularly on the cardiovascular and respiratory systems.

Scoliosis is usually classified as congenital, infantile, idiopathic, and paralytic. In the congenital type an obvious bony anomaly of the vertebræ, such as one or more hemivertebræ, is present at birth; there are often associated deformities, such as fusion of ribs, absence of ribs, or congenital heart lesions. Infantile scoliosis appears in the first six months of life, an age at which no bone abnormalities can be detected radiographically. About a third of these curves improve spontaneously; two-thirds become progressively worse with growth, ultimately producing an ugly and disabling deformity with severe lateral wedging of the vertebræ and gross rotation. The first type is probably due to malposition in utero without any basic vertebral defect. Curves of the second type are almost certainly "congenital"—that is, there is an inherent disorder of vertebral

1. Kent, E. M. *Amer. Rev. Tuberc.* 1942, **46**, 524.
2. Jones, E. M., Peck, W. M., Willis, H. S. *Amer. J. Dis. Child.* 1946, **72**, 296.
3. Hutchison, J. H. *Glasg. med. J.* 1949, **30**, 271.
4. Lander, F. P. L. *Thorax*, 1946, **1**, 198.
5. Lander, F. P. L., Davidson, M. *Brit. J. Radiol.* 1938, **11**, 65.
6. Findlay, L. *Arch. Dis. Childh.* 1935, **10**, 61.
7. Findlay, L., Graham, S. *ibid.* 1931, **6**, 1.
8. Lees, A. W. *Brit. med. J.* 1950, ii, 1138.
9. McNeil, C., Macgregor, A. R., Alexander, W. A. *Arch. Dis. Childh.* 1929, **4**, 170.
10. Robinson, W. L. *Brit. J. Surg.* 1933, **21**, 302.
11. Ogilvie, A. G. *Arch. intern. Med.* 1941, **68**, 395.
12. Churchill, E. D. *J. thorac. Surg.* 1949, **18**, 279.
13. Whitwell, F. *Thorax*, 1952, **7**, 213.
14. Williams, H., O'Reilly, R. N. *Arch. Dis. Childh.* 1959, **34**, 192.
15. *Lancet*, 1958, ii, 734.

growth potential. So-called idiopathic curves arise later in life, often around the age of nine or ten, particularly in girls, and usually become progressively worse with the growth spurt of early adolescence. There is pronounced vertebral rotation; the curve usually becomes fixed and rigid and the vertebræ wedge-shaped. Paralytic curves comprise mostly those which follow poliomyelitis. They fall into two main types. The first type mimics very closely the so-called idiopathic curve; commonly the deformity becomes apparent only some years after the original attack and then, with continued growth, becomes rapidly worse. In the other type there is extensive paralysis of the spinal muscles and what might be termed general collapse of the spine—either a long " C " or a double curve, such curves often remaining comparatively mobile, at any rate for some years.

Because so little is known of ætiology, rational preventive treatment is hardly possible. In the past few years the trend of thought has been largely in one direction—namely, that, whatever the primary ætiological factors, the governing factor in the development of severe scoliosis is unequal growth of the vertebral column—and treatment has been directed largely to preventing the deformity becoming worse when the spine's growth potential is clearly asymmetrical. Often, of course, scoliosis progresses relatively little, and no special treatment is required.

A recent issue of the *Bulletin of the Hospital for Joint Diseases*,[1] New York, is dedicated to the memory of the late SAMUEL KLEINBERG, who had been studying the problem of scoliosis since 1911. In KLEINBERG's writing [2] are embodied three main principles which are still applied in the treatment of scoliosis—namely: (1) retention and correction by means of mechanical braces, jackets, frames, and other devices; (2) spinal fusion to hold the spine in correction or to prevent the deformity getting worse; and (3) excision of the projecting ribs and transverse processes as a cosmetic procedure in the mature patient. The *Bulletin* includes notable contributions bearing on the ætiology of scoliosis and, in particular, a paper by PONSETTI [3] on Experimental Scoliosis describing the various ways in which scoliosis has been produced in animals, particularly by feeding them on diets which have been enriched with lathyrus seeds. Such diets cause a defect in the chrondroitin sulphate with loss of adhesion of the ground substance, loosening of the insertion of ligaments and muscles, and irregularity and disruption of the epiphyseal plate with epiphyseal slipping and scoliosis; often there are also defects of the sternum and arterial lesions. FARKAS [4] postulates that separation of the epiphyseal ring and its partial displacement represent the basic pathological process in scoliosis, and there are striking resemblances between the radiographic features of experimental scoliosis due to lathyrus and many examples of idiopathic scoliosis in man. Considerable research has been undertaken into the nature of the toxic agents in lathyrus peas, and a number of such agents have been discovered —notably β-amino-propionitrile, amino-acetonitrile, and methylene-amino-acetonitrile. It has been found, too, that semi-carbizide produces in laboratory animals scoliosis which is apparently very similar to that produced by these agents. Scoliosis has also been produced experimentally by unilateral irradiation of the spine and by holding animals' spines in a deformed position for several months. BICK,[5] who has made a special study of the histological appearance of the developing vertebræ, favours the hypothesis that the most important common factor in severe scoliosis is a disorder of the epiphyseal cartilage leading to asymmetical growth. Indeed, once a certain degree of fixed deformity has become established there must inevitably be greater pressure on the vertebral epiphyses on the concave side, and this will lead to unequal growth.

Some of these studies may seem rather remote from practical issues. This is partly true; but until we know the exact primary factors we cannot apply effective preventive treatment. Meanwhile, we can recognise cases in which the spinal deformity is likely to be severe and progressive, and take steps to prevent the deformity becoming worse. In the past, this has been achieved in three main ways. The first is by the application of jackets, plasters, braces, frames, or other splints. All such appliances depend for their effectiveness on one or other or a combination of two main actions—longitudinal traction and three-point pressure—and the most efficacious splint combining these two actions is probably the Milwaukee brace.[6] Nevertheless, this brace has disadvantages. It is cumbersome and unsightly; and by itself it does not effectively control severe progressive scoliosis, though it is very valuable in the collapsing type of paralytic curve or as an adjunct to surgical intervention in the convalescent phase. No appliance can take all pressure off the spine of an ambulant child.[7] Certain workers, notably COBB,[8] have advocated recumbency for up to two years during periods of rapid growth for children with progressive scoliosis; but there is a widespread feeling that conservative treatment alone does not control a severe progressive deformity. For many years attempts have been made to control progressive deformity of the spine by means of posterior fusion [8 9]. But this, too, seems to be only a partial answer. A spinal graft, once it has become incorporated, is plastic like any other growing bone [10]; and a spinal fusion, although it may delay and diminish deformity, does not prevent deformity where the forces of unequal growth are very strong [11]; indeed, in the presence of severe rotation, it may even act as a tether and aggravate the deformity. More recently, attempts have been made to control progressive deformity by destroying a number of epiphyseal growth cartilages on the convex aspect of the spine, combining this with fusion of the vertebral bodies on their convex aspect.[12]

1. *Bull. Hosp. Jt Dis.* October, 1958.
2. Kleinberg, S. Scoliosis. Philadelphia, 1951.
3. Ponsetti, I. V. *Bull. Hosp. Jt Dis.* 1958, **19**, 216.
4. Farkas, A. *ibid.* p. 260.
5. Bick, E. M. *ibid.* p. 225.
6. Blount, W. P. *ibid.* p. 152.
7. Lovett's Lateral Curvature of the Spine (edited by F. R. Ober and A. H. Brewster). Philadelphia, 1931.
8. Cobb, J. R. *Bull. Hosp. Jt Dis.* 1959, **19**, 187.
9. Risser, J. C. *ibid.* p. 166.
10. Cleveland, M., Bosworth, B. M., Fielding, J. W., Smyrmis, P. *J. Bone Jt Surg.* 1958, **40A**, 91.
11. Hallock, H., Francis, K. C., Jones, J. B. *ibid.* 1957, **39A**, 481.
12. Roaf, R. *Bull. Hosp. Jt Dis.* 1959, **19**, 120.

This method has not been used long enough or on a large enough scale for its final place in treatment to be determined. We must hope that further research will yield more exact knowledge of the ætiology of each type of scoliosis so that rational preventive measures can be instituted at the earliest possible stage and the need for heroic operations on patients with established severe deformities will ultimately disappear. So long as there are such patients we must try to do something for them; and, even though operations such as excision of the ribs and parts of the scapula may be regarded as purely cosmetic, in selected cases they bring great benefit and comfort to the patient.

The history of the treatment of scoliosis is largely the history of orthopædics itself, and, in particular, the history of the mental concepts that have dominated orthopædic practice. It is appropriate that this issue of the *Bulletin* should be dedicated to SAMUEL KLEINBERG, who, besides being an outstanding surgeon, was an authority on the history of the various types of splints and corrective appliances which have been used in the treatment of scoliosis throughout the ages.

## Annotations

### ENDOGENOUS HYPOGLYCÆMIA

"SPONTANEOUS" hypoglycæmia often provides a strenuous exercise in diagnosis.[1–3] Organic hyperinsulinism is perhaps the most readily understood cause. Hypoglycæmia may result from the therapeutic use of insulin; and the malingerer, the suicide, and the murderer have all used this knowledge for their own ends. (Another exogenous cause of hypoglycæmia—and one that is especially liable to be overlooked—is tobacco-smoking.[4])

Endogenous hyperinsulinism probably arises from either an islet-cell tumour [5] or hyperplastic islet tissue.[3 6] Insulin secretion may be stimulated normally by the level of sugar in blood reaching the pancreas, but the mechanisms by which the activity of an adenoma is controlled or by which islet tissue is rendered diffusely hyperplastic [5] are unknown. The degranulation in β cells surrounding a pancreatic adenoma, and the speed with which they recover after extirpation of the tumour, suggest that the adenoma's secretion of insulin is sufficient for all needs and that it suppresses the secretion of surrounding cells. The diagnosis of endogenous hyperinsulinism is based principally upon Whipple's [7] triad of persistently low fasting blood-sugar, cerebral disturbance in the fasting state, and relief of this by glucose. Garland [1] points out, however, that exceptions exist, and that clinical signs of hypoglycæmia may appear in the non-fasting state, that proven cases may have normal glucose-tolerance curves, and that random blood-sugar determinations may be unhelpful. Clinical abnormality may be provoked by starvation for twenty-four hours or more, especially if this is followed by vigorous exertion. He also states that blood-sugar levels lower than 30 mg. per 100 ml. are almost diagnostic of organic hyperinsulinism, but in children hypoglycæmia of this degree may be found in the not uncommon idiopathic infantile hypoglycæmosis of McQuarrie,[8] whether of leucine sensitive or insensitive type,[9] and in other ill-understood metabolic diseases. At laparotomy the gland must be searched with extreme care before excluding the presence of a single tumour and resecting the caudal half of the pancreas. When surgery is impossible or refused, the insulin-secreting cells may fail in response to injected pituitary growth hormone,[10] but a high-carbohydrate diet is usually effective. Such adenomas are not to be confused with those non-insulin-secreting tumours whose association with peptic ulceration,[11 12] watery diarrhœa with hypokalæmia,[13] and malabsorption [14] has been described recently.

Hypoglycæmia may also occur spontaneously after partial or total gastrectomy or vagotomy. Here the sudden absorption of glucose may be responsible for the symptoms, either by effecting changes in osmotic pressure or by provoking excessive secretion of insulin. In the dog the upper three-quarters of the gastric mucosa contains α cells; but no evidence exists that in man loss of such cells by gastrectomy causes hypoglycæmia, and neither this nor any other hypothesis explains why there may be a latent period of many months before symptoms develop.[1 15]

Other cases of endogenous hypoglycæmia have been termed functional, nervous, psychogenic, or psychosomatic. Here symptoms develop in patients who have had previous neurotic complaints, and it is suggested [1] that intestinal hurry and accelerated glucose absorption act as they do after gastrectomy. Such patients can often tolerate relatively large injections of soluble insulin without symptoms other than sweating and increased appetite. Conn and Seltzer [16] claimed that this was the biggest group—an experience that is probably not general. Hypoglycæmia may itself cause emotional changes, and accordingly it may be difficult to establish that the hypoglycæmia resulted originally from emotional disorder.

The neurological manifestations of hypoglycæmia are very varied. In addition to evidence of "sympathetic activity", they may take the form of transient disturbances of vision, with or without squint; temporary or recurrent dysphasia; rotatory vertigo, first described by Moorhouse [17] in 1956; hemiparesis; and gradual or sudden, short or protracted loss of consciousness, which occasionally results in irreversible cerebral damage with anoxic changes in the cortex, basal ganglia, and cerebellum. Motor-neurone disease with widespread muscle weakness, wasting, and fasciculation in a patient subject to episodes of disturbed consciousness should suggest the possibility of endogenous hypoglycæmia.[18]

As Farquhar pointed out, there is often no close relation between the blood-sugar level and the development of symptoms.[19] The newborn baby appears to be tolerant of profound hypoglycæmia,[20] and beyond this age the clinical response varies widely. Neurotic and epileptic patients may be less tolerant than others, but a single patient may respond differently to the same low blood-sugar level on different days.

1. Garland, H. *Brain*, 1958, **81**, 485.
2. Kinsbourne, M., Woolf, L. I. *Arch. Dis. Childh.* 1959, **34**, 166.
3. Douglas, D. M. *ibid.* p. 171.
4. Berry, M. G. *Ann. intern. Med.* 1959, **50**, 1149.
5. Nicholls, A. G. *J. med. Res.* 1902, **8**, 385.
6. Farquhar, J. W. *Arch. Dis. Childh.* 1959, **34**, 76.
7. Whipple, A. O. *J. int. Chir.* 1938, **3**, 237.
8. McQuarrie, I. *Amer. J. Dis. Child.* 1954, **87**, 399.
9. Cochrane, W. A., Payne, W. W., Simpkiss, M. J., Woolf, L. I. *J. clin. Invest.* 1956, **35**, 411.
10. Black, K. O., Macdougall, I., Reid, E., Young, F. G. *Lancet*, 1952, i, 19.
11. Zollinger, R. M., Ellison, E. H. *Ann. Surg.* 1955, **142**, 709.
12. Ellison, E. H. *Surgery*, 1956, **40**, 147.
13. Verner, J. V., Morrison, A. B. *Amer. J. Med.* 1958, **25**, 374.
14. Maynard, E. P., Point, W. W. *ibid.* p. 456.
15. Muir, A. *Brit. J. Surg.* 1949, **37**, 165.
16. Conn, J. W., Seltzer, H. S. *Amer. J. Med.* 1955, **19**, 460.
17. Moorhouse, D. *Brit. med. J.* 1956, ii, 1512.
18. Williams, C. J. *ibid.* 1955, i, 707.
19. Farquhar, J. W. *Arch. Dis. Childh.* 1956, **31**, 203.
20. Sakel, M. *Amer. J. Psychiat.* 1939, **94**, suppl. 24.

## INSECT STINGS

In the United States deaths are attributed to the bites and stings of venomous animals and insects at a rate of nearly one a week.[1] Even this is probably a conservative estimate, for sudden deaths due to stings may be ascribed to heat stroke or a heart attack if there is no clear history of a sting or if the local cutaneous reaction is overlooked.

During the five years 1950–54, 215 deaths in the United States were certified as due to the bites and stings of insects, snakes, scorpions, or spiders.[1] Various insects, including bees, wasps, yellow-jackets, hornets, and ants, accounted for two-fifths, and snakes for a third, of these deaths. Children and youths under 20 accounted for 44% of those who died from snake-bite, but only 7% of those who died from insect-stings. The clear predominance of fatal stings in adults suggests that host factors—perhaps the age of onset of insect allergy—play a part in the gravity of the effect. The interval between snake-bite and death was six to forty-eight hours, but after insect stings the interval was usually less than an hour. Such a short interval does not allow much scope for treatment, unless the patient happens to have immediate access to adrenaline.

Mueller [2] describes a case in which death was probably averted by a one-word history and diagnosis.

A telephone operator answered her light to hear a faint voice summoning a doctor's help. The call was traced, and a doctor found an unconscious woman beside the telephone with the word " stung " written on the telephone pad. She recovered after prompt administration of adrenaline. Within a few minutes of being stung by a wasp, she had become weak and dyspnœic. She had managed to reach the house, scribble " stung " on the pad, and telephone before losing consciousness.

Repeated minor stings may create a state of hypersensitivity in which each fresh sting produces a more severe reaction.[3] In such cases and in those of patients with an allergic diathesis prompt measures can be life-saving.

Marshall [3] has recounted the local and systemic effects of wasp and bee venom. Its chemical composition remains obscure, although various fractions, such as histamine, hyaluronidase, and a bradykinin, have been identified. Bee venom is known to have hæmolytic, hæmorrhagic, and neurotoxic effects in addition to its profound histamine activity. The local cutaneous reaction is the well-known triple response of redness, flare, and weal. Wasps, unlike bees, are scavengers and may also transmit infection; so the brawny induration of a wasp-sting may be due to associated cellulitis: hence, in addition to anti-histamine agents, antibiotics may be indicated in the management of the local reaction. The systemic reactions are of varied intensity; from his large personal experience Mueller [2] grades them into four groups. Reactions in the two lesser grades consist of urticaria, œdema, constriction of the chest, wheezing, and gastrointestinal upsets; in the third grade there is also dyspnœa, dysphagia, hoarseness, confusion, and a feeling of impending disaster; the most severe grade of reaction is evidenced by collapse, cyanosis, hypotension, incontinence, and unconsciousness. As a rule, the earlier the onset of symptoms after the sting, the more severe the reaction is likely to be. A general reaction may necessitate speedy administration of subcutaneous adrenaline, intramuscular anti-histamine, or even intravenous prednisolone; and desensitisation should be considered as a preventive measure. For this purpose Mueller [2] recommends whole-insect extracts rather than venom-sac contents, since the antigen causing reactions is present throughout the insect's body and the venom contains only a small amount. He also recommends that a mixed extract of equal parts of bee, wasp, hornet, and yellow-jacket should be injected, for the allergic individual may be susceptible to all types of stings. Mueller's scheme for desensitisation consists of gradually increasing weekly injections and thereafter maintenance doses every four to six weeks for up to three years. It would also seem advisable for the susceptible to carry with them during the summer months an emergency supply of isoprenaline tablets for sublingual use until they can reach a doctor.

1. Parrish, H. M. *A.M.A. Arch. intern. Med.* 1959, **104**, 198.
2. Mueller, H. L. *New Engl. J. Med.* 1959, **261**, 374.
3. Marshall, T. K. *Practitioner*, 1957, **178**, 712.

## THE CONVALESCENT EXCRETER OF SALMONELLÆ

Chronic carriage of salmonellæ, other than typhoid and paratyphoid bacilli, is rare. Clearance of the fæces after an attack of salmonella gastroenteritis is usually rapid in adults and older children, less than 10% of whom are infectious for more than six weeks.[1–4] In infants, however, the period of infectivity is often longer, and excretion for six to twelve months is common.[5,6] In the past, these healthy infant excreters were usually kept in hospital until a series of negative fæces cultures had been obtained, and they were a constant source of danger to others. Of recent years there has been a growing tendency to discharge them from hospital if the home conditions are good and the household does not include another small child or a food-handler. Some, however, must stay in hospital for many months, and an effective method of shortening the period of infectivity would save many hospital beds and greatly reduce the number of cross-infections in children's wards.

Unfortunately, laboratory tests give a misleading, and usually over-optimistic, idea of the value of antibiotics and other chemotherapeutic agents both in treating salmonella infections and in rendering convalescents non-infectious. For example, nearly all salmonellæ are susceptible in vitro to concentrations of chloramphenicol and of the tetracyclines that are readily attainable in the body; yet, whereas chloramphenicol has a powerful therapeutic effect on generalised salmonella infections, the tetracyclines have almost none.[7,8] In vitro sensitivity to streptomycin is variable, and the results of treatment are generally disappointing, even with sensitive strains. There is no convincing evidence that the administration of any of these antibiotics shortens the period of fæcal excretion, though the strains of salmonella isolated after an unsuccessful course of treatment are nearly always sensitive in vitro. The frequency with which sensitivity tests on salmonellæ are requested by physicians suggests that these facts are not widely appreciated.

Assessment of the value of any new drug in eradicating symptomless salmonella infections should, therefore, be based on observations made on human beings. The number of subjects in the trial must be large, because of the rapidity of natural clearance; the test and control groups must be comparable in age and possibly also in duration of excretion before treatment; and the chances of reinfection must be low.

1. Perry, H. M., Tidy, H. L. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1919, no. 24.
2. Mosher, W. E., Wheeler, S. M., Chant, H. L., Hardy, A. V. *Publ. Hlth Rep., Wash.* 1941, **56**, 2415.
3. Kwantes, W. *Mon. Bull. Minist. Hlth Lab. Serv.* 1952, **11**, 239.
4. Lennox, M., Harvey, R. W. S., Thomson, S. *J. Hyg., Camb.* 1954, **52**, 311.
5. Rubenstein, A. D., Feemster, R. F., Smith, H. M. *Amer. J. publ. Hlth*, 1944, **34**, 841.
6. Szanton, V. L. *Pædiatrics*, 1957, **20**, 795.
7. Knight, V., Sánchez, F. R., Sánchez, A. R., Shultz, S., McDermott, W. *Arch. intern. Med.* 1950, **85**, 44.
8. Watson, K. C. *Lancet*, 1955, i, 646.

Several new substances have been described which appear to have a powerful action on salmonellæ. The antibiotic synnematin B is active in vitro and in animals, and has yielded promising clinical results in the treatment of typhoid fever [9–11]; but little information is available yet about its effect on the duration of excretion. Furazolidone (N-[5-nitro-2-furfurylidene]-3-amino-2-oxazolidone) has been used extensively in the treatment of salmonella infections of birds. In bacillary white diarrhœa of chicks and in fowl typhoid (both due to *Salmonella gallinarum*), not only was there a striking therapeutic effect, but most chronic infections were eliminated; but with *Salm. typhimurium* infections of poultry most survivors became chronic carriers.[12–15] Information about the action of furazolidone on infections in man is scanty,[16] though the drug is already on sale in the United States and is being recommended for the treatment of diarrhœal diseases in general.. McMath and Hussain [17] have reported briefly on the treatment of salmonella infections with humycin, a broad-spectrum antibiotic which is administered orally but is not absorbed from the gut. Their results suggest that humycin may be more useful in shortening the period of fæcal excretion than other broad-spectrum antibiotics. A carefully controlled trial on a larger scale would be valuable.

## OTITIC MENINGITIS IN THE ANTIBIOTIC ERA

THE use of antibiotics in the treatment of acute otitis media has enormously reduced the incidence of mastoiditis and intracranial complications. But when such complications arise they are still potentially lethal. Moreover nowadays the signs tend to be more difficult to recognise, and the causal organisms are often resistant to the usual antibiotics. An investigation by Hara [18] at the Los Angeles County Hospital showed that otitic meningitis still carries the high mortality of 47% in children and 43% in adults.

Chronic suppurative otitis media is a different disease ætiologically, pathologically, and clinically. The benign type, with painless mucoid discharge issuing from a large central perforation, is becoming less common as a result of greater attention to general, nasal, and aural hygiene. It very rarely leads to complications apart from diminution of hearing. The second type, which now forms the majority of " chronic ears " seen by the otologist, is far from benign. It is characterised by painless, purulent, offensive discharge from an attic or high posterior tympanic perforation, caused by a cholesteatoma in the epitympanic space. This narrow recess is progressively expanded by the relentlessly enlarging ball of desquamating epithelium and dead leucocytes until its bony walls are breached. The infection is then carried into the meninges and brain, either directly across the tegmen tympani or indirectly via an infected labyrinth, and by retrograde septic venous thrombosis.

Hara [18] investigated a series of 28 adults with otitic meningitis seen over a period of eight years. No less than 23 of these cases were secondary to chronic suppurative otitis media, and in 10 death resulted. Of the 28 patients, 4 had undergone simple or radical mastoidectomy, which had not eradicated the disease. In acute, overwhelming meningitis no time can be lost; and intensive chemotherapy, often with multiple antibiotics, was applied. As soon as the meningitis was brought under control the infective focus in the middle ear was eradicated; radical mastoidectomy was undertaken in all cases.

Hara stresses the seriousness of this complication. Those who survived spent an average of 45 days in hospital. Otitic meningitis is preventable. Every patient with chronic attic suppuration runs the danger of intracranial disaster; and it is time we realised that in such cases no antibiotic is a substitute for a well-performed operation on the temporal bone, which not only eradicates the infective focus but also seeks to restore the damaged hearing by tympanoplasty.[19]

## PHARMACEUTICAL MONOPOLIES AND RESEARCH

PATENT legislation was discussed by Mr. H. Treves Brown [20] in his address as chairman of the British Pharmaceutical Conference at Bournemouth on Sept 21. Such legislation was originally introduced to prevent James I from filling his Treasury by selling monopolies. Subsequent refinements of the law have all aimed at a balance between ensuring that the inventor is rewarded and enabling the public to use the invention. In 1919 Britain abandoned product patents—a monopoly on a substance could no longer be secured, but a method of manufacture could still be protected. From 1919 to 1949, when the law was again changed, the chemical industry was able to manufacture by alternative methods, where these could be devised, rather than pay royalties. Perhaps the resultant preoccupation with process techniques may partly explain the relatively slow progress of pharmaceutical research in Britain.

The failure to protect penicillin by patents was not just an unfortunate oversight; and the experience with penicillin suggested to some the desirability of patenting the saleable results of research. The pharmaceutical industry can reasonably contend that, if it is to apply its research efforts at the points where the need is greatest, it should be assured of a reasonable return. Mr. Treves Brown supports the view that the patent law should be strengthened.

A more difficult, but no less urgent, problem concerns the choice of research projects by pharmaceutical firms, which at present tend to concentrate on remedies for common conditions. Perhaps the solution adopted for the aircraft industry—of Government contracts supporting the cost of desirable but commercially unattractive investigations—could be adapted to pharmaceutical research.

9. Olson, B. H., Jennings, J. C. *Antibiot. Chemother.* 1954, **4**, 11.
10. Olarte, J., Figueredo, G. *ibid.* 1955, **5**, 162.
11. Benavides, V. L., Olson, B. H., Varela, G., Holt, S. H. *J. Amer. med. Ass.* 1955, **157**, 989.
12. Smith, H. W. *Vet. Rec.* 1954, **66**, 493.
13. Smith, H. W. *ibid.* p. 215.
14. Smith, H. W. *ibid.* 1955, **67**, 749.
15. Wilson, J. E. *ibid.* p. 849.
16. DeLeon, E. P. *Antibiot. Med.* 1957, **4**, 814.
17. McMath, W. F. T., Hussain, K. K. *Publ. Hlth*, 1959, **73**, 328.
18. Hara, H. J. *Ann. Otol., &c., St. Louis*, 1959, **68**, 305.
19. Wullstein, H. *ibid.* 1956, **65**, 1020.
20. *J. Pharm. Pharmacol.* (in the press).

Prof. JOHN KIRK, who formerly held the Courtauld chair of anatomy at the Middlesex Hospital, died on Sept. 26 at the age of 77.

### INDEX TO THE LANCET

THE index and title-page to vol. I, 1959, which was completed with the issue of June 27, is enclosed with each copy of our present issue. This practice will be followed with future indexes; and accordingly those who wish to receive the index need no longer apply to our office.

## Special Articles

# AN EPIDEMIC OF POSTOPERATIVE WOUND INFECTION BY TYPE-80 STAPHYLOCOCCI

A. A. B. MITCHELL, B.Sc. Glasg., BACTERIOLOGIST
MORAG C. TIMBURY, M.B. Glasg., REGISTRAR IN BACTERIOLOGY
J. B. PETTIGREW, M.B., B.Sc. Glasg., A.R.I.C., CONSULTANT BIOCHEMIST
J. G. P. HUTCHISON, M.D. Lond., LECTURER IN BACTERIOLOGY

*From the Bacteriology Department of the University of Glasgow*

THE epidemic here described illustrates (1) the danger of a surgeon's operating while suffering from septic lesions, and (2) the extent to which the unusually dangerous *Staphylococcus aureus*, phage-type-80, may spread when introduced into a surgical unit.

The epidemic began in a surgical unit of six wards containing 180 beds. The unit is staffed by six surgeons who do general surgical work, including urology. The wards are single-storey buildings connected by long airy corridors which have windows and doors opening on the hospital grounds. A newly built operating theatre serves both the surgical unit and a gynæcological unit in the hospital. It is well designed and equipped and has a positive-pressure ventilation system.

### The Start of the Epidemic

Before the epidemic wound sepsis in the unit was infrequent, but not recorded. No one of the six surgeons appeared to have a significantly higher incidence than any other. In 1958, six weeks before the epidemic, we began, as a matter of interest, routinely to phage-type the staphylococci isolated from infected surgical wounds. This revealed that several different strains of staphylococci, most of which belonged to phage-group III, were responsible for the infections. At that time there was no evidence of an epidemic strain.

During May, 1958, however, one surgeon, Mr. A, noticed a sudden rise in his sepsis-rate, in that 9 of his 51 cases (18%) developed wound infections. Since most of the infections were deep wound abscesses it was thought that they must have been acquired at operation. At this point the surgeon told us that since the end of April he had been suffering from a series of boils affecting both axillæ and that he had operated on all the infected cases during the course of these infections. Phage-typing showed that all the infected cases were due to type-80, and this same type was isolated from one of surgeon A's axillary boils in May. There was therefore little doubt that surgeon A had infected these cases from his axillary boils during operation.

Shortly after this outbreak it was realised that there had been a smaller but similar outbreak of wound infection among surgeon A's cases in March, when 5 of 45 of his patients developed wound infection. At the end of February surgeon A had gone off duty with a septic finger. The infected patients had been operated on when he returned to work when the lesion was scabbed over. Although no phage-typing was being done in March, 1958, the staphylococci from these infections and from surgeon A's finger had the antibiotic sensitivity pattern of the epidemic type-80 strain (i.e., resistant to penicillin and the tetracyclines, sensitive to chloramphenicol and erythromycin, and variable in sensitivity to streptomycin). Later, in June, type-80 was isolated from one of the patients operated on in March who had a chronic discharging wound. This evidence therefore suggested that the March outbreak was also caused by type-80, in this instance derived from surgeon A's scabbed-over septic finger, and that his axillary boils in May were due to the same staphylococcal type as this earlier infection. It is interesting that in the interval between episodes of sepsis, when he was presumably still harbouring the organism, surgeon A did not transmit it to his patients.

### Secondary Spread

Shortly after the first small outbreak of infection in March phage-typing was begun. This showed that there had been no secondary spread of type-80 in the surgical wards at this time. A widespread epidemic of wound sepsis, however, followed the second appearance of the strain in surgeon A's cases in May, and a further 47 cases of wound infection due to type-80 appeared during the succeeding seven months. The first 2 secondary cases of wound infection were found in May after the outbreak in surgeon A's cases. They were apparently due to cross-infection since they followed operations performed by different surgeons. Similarly, in the secondary epidemic, wound infections were associated with all six surgeons in the unit. Although the infections appeared among patients in each of the surgical wards, two wards were more severely affected than the other four.

The table records the monthly incidence of wound infections due to type-80 and the proportion of the surgical wounds at risk which became infected.

NUMBER OF OPERATIONS PER MONTH FOLLOWED BY WOUND INFECTION DUE TO TYPE-80

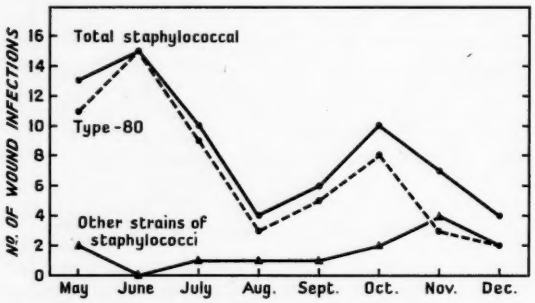
| Month | Total of surgical operations | No. of operations followed by type-80 infection | % of wounds at risk which became infected with type-80 |
|---|---|---|---|
| May | 335 | 11 | * |
| June | 301 | 15 | 5 |
| July | 245 | 9 | 4 |
| August | 262 | 3 | 1 |
| September | 306 | 5 | 2 |
| October | 301 | 8 | 3 |
| November | 276 | 3 | 1 |
| December | 301 | 2 | 1 |

* The percentage of operation wounds in May becoming infected with type-80 was not calculated, because all except 2 of the infections appeared in cases operated upon by surgeon A.

It may be seen that after the introduction of type-80 in surgeon A's cases in May the sepsis-rate of the unit in June and July was 5% and 4% respectively. In August, when various measures had been instituted in an attempt to reduce the number of infections, it fell to a low level and remained low during the next four months (from September to December). No type-80 infections appeared in January, 1959. The epidemic in the surgical unit therefore lasted eight months, and though the number of infected cases in each month was not large the morbidity among these patients was considerable.

The figure shows the monthly incidence of all staphylococcal wound infections in relation to the incidence of those due to type-80 and of those due to other strains of staphylococci. In the first four months type-80 was clearly predominant as a cause of wound infection; but as the epidemic waned in the later months, wound infections due to other strains of *Staph. aureus* began to appear more frequently.

Most of the infections in the epidemic were wound infections, but type-80 also gave rise to other forms of septic lesion in 11 patients.




**Monthly incidence of wound infections due to type-80 in relation to those due to other staphylococcal strains.**

Of 4 patients who had wound infections, 3 later suffered from boils, and 1 developed an abscess of the thigh. 1 patient whose wound was not infected also suffered from boils. 4 patients had infections of the urinary tract: 3 became infected after being catheterised, and the 4th, who had the urinary infection before operation, later suffered from wound sepsis due to the same organism. Type-80 was the cause of fatal parotitis and suppurative otitis media in one elderly patient and was isolated from the stool of another who had undergone prostatectomy and developed severe postoperative diarrhœa.

Apart from surgeon A, only one member of the hospital staff is known to have become infected with type-80 during the epidemic period. This was a nurse in the out-patient department who developed a septic finger.

9 surgical patients who had infections due to type-80 died, but in 5 death was mainly due to other causes. Although type-80 materially contributed to the deaths of the remaining 4, their general condition had previously been poor and it is probable that the supervention of any infection would have hastened death.

### Infections by Related Type

The staphylococcal strain type-52/52A/80 has been observed to be closely related to type-80 (Rountree and Beard 1958). During the present epidemic this strain was isolated from 4 surgical patients—from 3 who had wound infections and a 4th who had parotitis. A nurse working in one of the surgical wards also developed a septic finger due to the strain.

### Type-80 in the Hospital Environment

In August, nasal swabs were taken from the entire staff of the surgical wards. This included surgeons, anæsthetists, nurses, orderlies, and domestics. A total of 114 nasal swabs were collected and 7 nurses were found to be carrying the epidemic strain. Six of the nurses worked in the surgical wards but the 7th was a theatre sister. Further inquiries, however, showed that she could not have been responsible for the spread of the epidemic strain because she had assisted at only 4 of the operations which were followed by sepsis. The rather low carriage-rate (6%) of type-80 in the nursing staff in spite of ward contamination may have been due to the rotation of the nurses among other units. Three nurses were also found to carry the related strain type-52/52A/80 in their noses. Samples were taken from blankets and floor dust of the two wards which were most affected by the epidemic and yielded strains of type-80.

### Source of the Wound Infections

The most striking feature of the type-80 wound infections in the secondary epidemic was that the majority were deep wound abscesses and therefore appeared to have been acquired during operation rather than in the wards postoperatively. There was no demonstrable source of infection in the operating-theatre. Moreover, there had been no type-80 infections among the gynæcological cases for which the theatre was also used. Hence it was unlikely that the theatre itself, or the nurses there, could be responsible for the spread of type-80.

The possibility remained that the patients were themselves carrying the epidemic strain from the wards into the theatre. In the present epidemic no investigations were undertaken to estimate the staphylococcal skin and nasal carriage in patients before operation and there was therefore no direct evidence that this was a common route of infection. Nevertheless there were reasons for thinking that it was an explanation of the theatre-acquired infections. Firstly, type-80 was known to have contaminated the ward environment, and, as all the wards contained cases of sepsis due to it, there were obvious sources of infection within them; secondly, the wards with most cases of sepsis continued to show more new infections than the others; and thirdly, no source of infection could be found within the operating-theatre.

We learnt by chance of another way in which ward contamination could be brought into theatre from the wards.

It was discovered that clean linen was returned to the wards in the basket which had delivered soiled linen to the laundry. A swab was taken from one of these baskets and yielded a type-80 staphylococcus. Patients were sent to theatre dressed in socks, and in a "clean" gown (from the soiled-linen basket) which during operations was folded up under the patients' arms. The gown, with its possible contamination, would therefore be placed only a few inches from the wound during abdominal operations. The arrangements for delivery of clean laundry were altered as soon as this state of affairs was discovered and now linen is sent to and from the laundry in washable canvas hampers.

### Control of the Epidemic

The first step was to rid the affected surgeon of his recurrent infections. This proved to be extremely difficult.

As he was a nasal carrier, he began intranasal treatment with neomycin-bacitracin cream, and he was advised to wash with hexachlorophene soap both in hospital and at home. After a short course of the intranasal antibiotic, his nasal swabs became negative and he resumed operating. His boils, however, recurred while he was away on holiday, and on returning he was once again unable to resume operating because of a boil on his finger due to type-80. Further treatment with the intranasal antibiotic cream and the antiseptic soap was then carried out: in addition his clothing was washed with a quaternary ammonium disinfectant and all outer garments were dry-cleaned (it was hoped that the steam pressing would destroy any staphylococci contaminating them). Despite these measures type-80 was isolated from surgeon A's hands three weeks later although his boils were then healed. Had one recurrence not coincided with his holiday he would have been absent from duty with recurrent boils for three months out of six.

This history illustrates how hard it is to be certain of curing recurrent sepsis in any individual, and also the enormous inconvenience which may be caused to a surgeon.

When it was recognised that type-80 was causing a general epidemic a very strict aseptic technique was begun in the wards to avoid cross-infection during dressing rounds.

All nasal carriers of type-80 among the nurses of the surgical unit were sent off duty and treated with neomycin-bacitracin

cream. Later, at the end of August, the surgeons were asked to use a hand rinse of 0·5% chlorhexidene in 70% alcohol just before donning surgical gloves. The efficacy of the hand rinse was demonstrated on one occasion when we asked surgeon A to scrub up and don surgical gloves for two hours—once with and once without the chlorhexidene hand rinse. Type-80 was isolated from his hands and the inside of his gloves when he omitted the hand rinse but no *Staph. aureus* was isolated when it was used.

These measures were followed by a sharp fall in the incidence of type-80 infections during and after August.

### Discussion

This epidemic shows again how much sepsis can be caused by a surgeon operating when he has a septic lesion. In an outbreak previously described (McDonald and Timbury 1957) severe wound infections in 6 patients were traced to a surgeon having a boil on his forearm. In that instance the epidemic strain was type-52A/79 and no widespread epidemic followed in the surgical unit concerned. In the present outbreak the infecting strain was type-80, which, after its appearance in the surgeon's own cases, became the predominant cause of postoperative sepsis in the unit. There was evidence that a similar smaller outbreak, probably also due to type-80, had preceded the major outbreak by two months but without secondary spread. It is noteworthy that the surgeon infected his cases only when he had a septic lesion—not when he was merely carrying the epidemic strain. This is further suggestive evidence of the danger from organisms derived from active lesions as distinct from those carried on the healthy skin or nasopharynx.

The site of the surgeon's lesions in the present outbreak was interesting. Septic lesions on hands or forearms are an obvious risk, but the danger of spread from a lesion in the axilla may not be so apparent. It is well known that the skin surrounding discharging lesions is heavily contaminated with the infecting organism. Staphylococci from the axillæ may spread down the arm inside the sleeves of surgical gowns or everyday clothing —in sweat, air currents, or by other means—to contaminate the forearm and hands. Spread from there to the patients' wounds may have been through glove punctures or wet gown sleeves or possibly by dissemination into the air. Colebrook and Ross (1947) found that *Streptococcus pyogenes* from a scabbed lesion on a surgeon's arm was disseminated into the air, and this may represent an important route for spread of organisms from a staphylococcal lesion also.

The history of recurrent sepsis in this particular surgeon emphasises the unsatisfactory state of treatment of this condition and also the inconvenience both to the surgeon and to the hospital deprived of his services during the episodes of sepsis. Nevertheless the danger of infecting wounds at operation is so great that no surgeon should ever operate while suffering from sepsis of hands or arms. Even in the absence of direct evidence, we regard boils anywhere as a surgical hazard of unknown magnitude. Before operating, a surgeon suffering from this form of sepsis should first ascertain that his hands are not contaminated and should make use of hand rinses such as have been described.

Type-80 has been described as a strain which causes more extensive epidemics than any other staphylococcus and which often produces a high incidence of skin lesions (Williams 1959). In the present epidemic, however, the incidence of skin sepsis was relatively low and most of the infections were wound infections.

Robertson (1958) has recommended that separate containers be provided for clean and soiled linen, and in the present epidemic the isolation of type-80 from a ward laundry basket, which was used for the transport of both clean and soiled linen, emphasises the importance of this. This indefensible practice was continuing at a time when special precautions were being taken to prevent the further spread of infection, and it shows the necessity of supervising carefully all details of ward hygiene.

Staphylococcal infection can be prevented only by a stricter aseptic regime than obtains in the wards and operating-theatres of most hospitals today. This should include, as a measure of the first importance, the suspension from duty of all members of staff who are suffering from staphylococcal sepsis.

### Summary

1. This paper describes an epidemic of postoperative wound infection in a surgical unit due to *Staphylococcus aureus* phage-type-80.

2. The epidemic strain first appeared in wound infections of patients operated on by a surgeon while he was suffering from septic lesions due to type-80.

3. Thereafter type-80 became the predominant cause of infection throughout the unit, and it persisted as the most common infecting organism for eight months.

4. Although type-80 gave rise to other forms of sepsis in a few patients, most of the infections were deep wound infections.

5. Contamination of the patients' skin or clothing by organisms acquired before operation, either in the wards or from contaminated laundry, was the probable source of many secondary cases of infection. The isolation of the epidemic strain from a laundry basket used for transporting both clean and dirty linen emphasises the need for careful supervision of all details of hospital hygiene.

6. Attention is again called to the danger of a surgeon's operating while he is suffering from septic lesions.

We should like to thank the surgeons and nurses of the hospital for their help in these investigations and also Mr. D. B. Coquhoun and Miss Clemence K. Hedges, B.SC., for their assistance with the phage-typing.

REFERENCES

Colebrook, L., Ross, W. P. D. (1947) *Lancet*, ii, 792.
McDonald, S., Timbury, M. C. (1957) *ibid*, ii, 863.
Robertson, H. R. (1958) *Ann. R. Coll. Surg. Engl.* **23**, 141.
Rountree, P. M., Beard, M. A. (1958) *Med. J. Aust.* ii, 789.
Williams, R. E. O. (1959) *Lancet*, i, 190.

## INDUSTRIAL REHABILITATION OF MALE CHRONIC SCHIZOPHRENIC PATIENTS

J. K. WING
M.B. Lond., D.P.M.

MEDICAL RESEARCH COUNCIL SOCIAL PSYCHIATRY RESEARCH UNIT, INSTITUTE OF PSYCHIATRY, MAUDSLEY HOSPITAL

R. G. T. GIDDENS

REHABILITATION OFFICER, WADDON INDUSTRIAL REHABILITATION UNIT, MINISTRY OF LABOUR

THERE are now about 64,000 men in mental hospitals in England and Wales. About three-quarters of them have been in hospital continuously for more than two years. Of these long-stay patients, the number under fifty years of age suffering from schizophrenia is about 12,500. A substantial proportion of such patients require very little nursing and supervision: their main need is adequate occupation (Cross et al. 1957, Garrett et al. 1957). This paper describes an experiment in which patients thought to be representative of this group attended a course at a

specialised industrial rehabilitation unit (I.R.U.) of the Ministry of Labour.

During 1956 about 4% of all entrants to the fifteen industrial rehabilitation units had had a psychotic illness. The proportion of these leaving prematurely was 27%, compared with a rate of 19% for all entrants. Of the psychotic entrants who completed the course, 56% were satisfactorily employed six months later, compared with 62% of the others (Ministry of Labour 1958). Jones (1956) described the work of the I.R.U.s for 208 resident patients from twenty-nine mental hospitals and mental-deficiency institutions. Of those completing the course 65% were satisfactorily employed six months later.

We recognised that similar results might not be achieved with chronic schizophrenic patients, whose rehabilitation is notoriously difficult. But the figures encouraged experiment.

## OUR EXPERIMENT

The physician-superintendent of Long Grove Hospital, Epsom, was asked to select 30 male schizophrenic patients, aged twenty-five to forty-five, who were occupied without close supervision and had been in hospital for more than two years. No other specification was made as to behaviour or mental state.

A psychiatrist unconnected with the project was asked to see all the patients and to rate the mental state of each for the following factors: flatness or incongruity of affect, thought disorder, delusions, and hallucinations. On the basis of these ratings the patients were divided into two categories—severely disturbed and moderately disturbed. From these categories patients were allocated to two groups, one of 20 patients who were to proceed to the I.R.U., the other a control group who remained in hospital on their usual routine. In addition, attitude to discharge and plans for the future were rated on a five-point scale. Only 5 of the experimental group, and 2 of the control group, had any kind of constructive plan for leaving hospital. Fitness for discharge was assessed by the consultant physicians looking after the patients. The groups were comparable in this respect. Only 3 patients were thought likely to be discharged within six months. Ratings of social withdrawal and socially embarrassing behaviour were also obtained.

2 patients originally in the experimental group were later rejected—one because he escaped from hospital and was thereafter placed under close supervision, the other because he had to remain in the hospital for physical treatment. They were replaced by 2 others fulfilling the original criteria.

At the beginning of the experiment the two groups were statistically comparable in respect of age (mean 35·3 years), age of onset (mean 25·3 years), length of stay in hospital (mean 5·3 years), highest previous occupation, marital status, legal status, and availability of interested relatives.

The patients were admitted to the I.R.U. a few at a time. They travelled to and from the hospital by hired bus, accompanied by a nurse. This procedure had disadvantages; for it showed from the outset that they were exceptional, and they came to be known as "Long Grove patients". In addition, no test was possible of their individual time-keeping, though this was later arranged for some. No special supervision was arranged at the I.R.U.: this is in any case fairly close. The patients were told that they were attending voluntarily and could leave the course whenever they wished. They were paid the usual money given to all I.R.U. entrants, but this was sent to the hospital, which deducted board and lodging and gave the remainder (about £1 weekly) to the patient. It was found convenient to reclassify many of the certified patients, once they had proved their reliability, as voluntary patients.

## RESULTS

At the time of follow-up (six months to a year later) 8 patients from the experimental group were working and none from the control group. The results in the two categories of the experimental group and in the control group were as follows:

*Moderately Disturbed* (*10*)

3 patients (including 2 still resident in hospital) were taking training courses (in tailoring, plumbing, and bench-fitting). 5 others had jobs which seemed so far to be satisfactory, and they gave satisfaction. Of the remaining 2 patients, one had left hospital and was keeping himself on National Assistance: he was no trouble to anyone but he was not working. The other, who had been in hospital twenty years, was still there and had no wish to work, though he was capable of working, as he showed at the I.R.U.

*Severely Disturbed* (*10*)

One patient was discharged from hospital and worked satisfactorily for several months, but had to be readmitted because of a relapse of his paranoid illness. His illness had previously been intermittent and it seems probable that the I.R.U. course fitted into a remission and had no relevance to the outcome. Another patient, who was originally very incoherent and volunteered florid delusions, improved considerably while at the I.R.U., and continued to improve afterwards. He was discharged but did not find work. A third seriously ill patient found work locally while continuing to live in hospital, but did not keep this job for more than two months.

5 patients improved sufficiently at the I.R.U. to win a recommendation for sheltered employment, perhaps in Remploy, Ltd. It was thought that they might continue to improve until they could be discharged from hospital to full-time work in open industry. However, no such sheltered employment could be found for them.

*Controls* (*10*)

Only 1 of the control group was discharged from hospital during this time, and he was later readmitted.

An attempt to measure some of the handicaps of these patients showed that socially embarrassing manifestations in their behaviour decreased significantly, as did abnormal mental phenomena rated at interview. There was a tendency towards improvement in attitude to work, which did not quite reach significance. Social withdrawal did not change in either direction.

## DISCUSSION

This was only a pilot experiment with small numbers, and the follow-up is not yet long enough for a firm assessment. Two administrative points, however, seem worthy of further investigation.

8 out of 20 patients, selected according to the criteria specified, and therefore possibly representative of a substantial number throughout the country, were completely or partially resettled after a routine I.R.U. course. We do not suggest that they could not have been resettled without such aid, since the experiment was not designed to answer this question. But, given the existing hospital services, it is doubtful whether more than 2 would have been discharged if the groups had not gone to the I.R.U.

Another 8 improved enough to justify the hope that further rehabilitation might lead to their eventual resettlement. But long-term rehabilitation is not at present obtainable for them. Should the results be repeated on a larger scale, there would be a strong case for creating new services.

If sheltered employment cannot be provided, selection of patients will depend on the severity of their illness.

According to the criteria used here, the " moderately " ill do comparatively well, even compared with non-psychiatric patients: in fact, since none of the group failed to complete the course, they did better than average. But all our patients were volunteers, which means that the large group of patients who want to remain in hospital was not represented. (In a recent survey by one of us, 40 out of 101 chronic schizophrenics interviewed said that they would prefer to stay in hospital.)

The following are possible reasons for the patients' improvement.

1. The I.R.U. enables the patient's working ability to be demonstrated to his doctor, the I.R.U. staff, the D.R.O., and potential employer, as well as to the patient himself. The resulting changes in attitudes are mutually reinforcing.

2. The realistic setting and the presence of non-schizophrenic workers make the adoption of a new role more possible.

3. Certain habits of working are deliberately inculcated, and the protective atmosphere of the hospital is minimised.

These three factors would be difficult to reproduce in the setting of a mental hospital. They exert considerable social pressure on the patient and may explain the decrease in manifestation of socially embarrassing behaviour. In turn, the patient increases in social " acceptability " as an employee, and as a person in general. However, there is no increase in social interaction: the patients preferred to keep to themselves, on the whole, though they were not actively unsociable.

These factors are also important for the progress of other kinds of patients, though emphases are placed differently. Almost all the difficulties encountered with this group of chronic schizophrenic patients have been often encountered before, except that 4 severely ill patients, who were unsuitable to be at the I.R.U. would not normally have been accepted. After the last patient had left the unit, nearly all the supervisors replied favourably to a questionnaire on the employability of chronic schizophrenics, which is a further sign of the success of the experiment. There is a strong case for repeating it on a larger scale.

SUMMARY

20 male schizophrenic patients, aged twenty-five to forty-five, all of whom had spent over two years in hospital, received a course of rehabilitation at an industrial rehabilitation unit of the Ministry of Labour. Half were severely disturbed, but none had needed special supervision in hospital. 10 matched patients served as controls.

The experimental group, as compared with the control group, showed significant improvement in mental state and behaviour. There was no change in social withdrawal.

8 of the experimental group were partially or completely resettled—all had been only moderately ill on admission to the I.R.U. 5 of the 10 severely ill patients in the experimental group showed their ability to work well under sheltered conditions. No member of the control group was resettled.

These results justify repetition of the experiment on a larger scale.

We are indebted to Dr. A. B. Monro, physician-superintendent of Long Grove Hospital, and to his staff for their cooperation in this experiment. Full acknowledgment is also due to the members of the I.R.U. staff.

REFERENCES

Cross, K. W., Harrington, J. A., Mayer-Gross, W. (1957) *J. ment. Sci.* **103**, 146.
Garrett, F. N., Lowe, C. R., McKeown, T. (1957) *Brit. J. prev. soc. Med.* **11**, 165.
Jones, M. (1956) *Lancet*, ii, 985.
Ministry of Labour (1958) *Minist. Lab. Gaz.* August.

## ELECTION CANDIDATES

THE lists of candidates include the names of the following medical men and women:

LONDON BOROUGHS

*Hampstead.*—D. T. Pitt, M.B. Edin. (Lab).
*Lambeth (Brixton).*—Brian Warren, M.R.C.S. (C).
*Wandsworth (Clapham).*—A. J. Glyn, B.A. Cantab., L.M.S.S.A. (C).
*Wandsworth (Streatham).*—D. L. Kerr, M.R.C.S. (Lab).

PROVINCES

*Basingstoke.*—L. G. Housden, M.D. Lond. (L).
*Batley and Morley.*—*A. D. D. Broughton, M.R.C.S. (Lab).
*Brentford and Chiswick.*—H. B. O. Cardew, L.M.S.S.A. (Lab).
*Carlisle.*—*Donald Johnson, M.R.C.S. (C).
*Cheltenham.*—K. G. Pendse, M.R.C.S. (Lab).
*Farnham.*—Joseph Greenwood-Turner, M.R.C.S. (Lab).
*Gosport and Fareham.*—*R. F. B. Bennett, B.M. Oxon. (C).
*Lichfield and Tamworth.*—F. R. Roberts, M.B. Birm. (C).
*Loughborough.*—*J. D. Cronin, F.R.C.S. (Lab).
*Luton.*—*Charles Hill, P.C., M.D. Cantab. (L. and C).
*Portsmouth West.*—Maxwell Bresler, M.R.C.S. (Lab).
*Ripon.*—*Sir Malcolm Stoddart-Scott, M.D. Leeds (C).
*Stoke-on-Trent, Central.*—*Barnett Stross, M.B. Leeds (Lab).
*Tiverton.*—J. E. O. Dunwoody, M.R.C.S. (Lab).
*Warrington.*—*Edith Summerskill, P.C., M.R.C.S. (Lab).
*Worcestershire, South.*—E. H. L. Harries, M.R.C.S. (L).
*York.*—D. R. L. M. Poirier, M.R.C.S. (Lab).

WALES

*Denbighshire, Denbigh.*—D. Alun Jones, M.B. Lpool (Plaid Cymru).

SCOTLAND

*Greenock.*—*J. D. Mabon, M.B. Glasg. (Lab and Coop).
*Perth and East Perthshire.*—R. D. McIntyre, M.B. Edin. (Scot Nat).

C, Conservative. Coop, Cooperative. Lab, Labour. L, Liberal. Scot. Nat, Scottish Nationalist. Plaid Cymru is the Welsh National Party.
* A candidate who was a member of the last Parliament.

# Public Health

## CONTROL OF ANTHRAX

### Suggestions based on Survey of Imported Hides

ANDREW B. SEMPLE
V.R.D., M.D. Glasg., D.P.H.
MEDICAL OFFICER OF HEALTH, CITY AND PORT OF LIVERPOOL

T. L. HOBDAY
M.B. Lpool, D.P.H.
SENIOR MEDICAL OFFICER, PORT OF LIVERPOOL

IN 1958 more than 122,000 cwt. of dry hides were imported through the port of Liverpool, and over the previous ten years the yearly average was 289,000 cwt. The chief exporting countries are Argentina, East Africa, and West Africa—countries in which anthrax is enzootic with epizootic incidents. Yet, judging by the rarity of the disease in Liverpool, the hazard to dock-workers seems to be slight. There were only 7 cases in 1954–58:

3 were in dock-workers handling dry hides; 2 in manual workers in a Government wool-disinfecting station; 1 in a joiner who worked in a dock shed; and 1 in a general labourer in a fertiliser factory. Only the last case was fatal.

As it is hard to assess the danger of imported hides by clinical results alone, it was decided in 1958 to sample dry hides systematically immediately after discharge from ships. Over a thousand separate samples were taken and classified by country of origin, type of hide, and commercial grading.

### Investigation

*Methods*

In a busy dock shed it is difficult to maintain the sterile precautions necessary for bacteriological sampling; but the following procedure was thought to be effective.

The sampling equipment consisted of small sterilised 1 oz. glass jars with rubber tops, a supply of 4 in. paper squares, and separate single-edged razor blades for each sample. Samples were taken by grasping some hair from the hide in the paper, taking care not to touch it with the hands: the razor blade was then used to free the hair from the hide, and scrapings from the base of the hairs were added to the sample, which was then carefully placed in a jar and sealed. The razor blades and the pieces of paper were collected in a separate part of the sampling box. The paper was later burnt and the razor blades re-sterilised. The glass jars were numbered, and a key related the samples to the actual hides examined.

The samples were sent to the laboratory in 1 oz. bottles. Caustic-potash solution (1 ml. of 15% caustic potash to 100 ml. of sterile water) was added to the material, stirred with a glass rod, and allowed to stand for two or three hours. The wash was removed and neutralised to phenol-red with 8% hydrochloric acid.

The wash was centrifuged for half an hour at 3000 r.p.m. The supernatant was poured off and 1 ml. of physiological saline solution was added to the deposit. The bottle was heated for five minutes at 65°C and 1 ml. of the deposit suspension was then inoculated intramuscularly into a guineapig.

All guineapigs were protected the previous day with 0·75 ml. polyvalent gas-gangrene antitoxin, containing 1000 units *Clostridium perfringens* antitoxin, 500 units *Cl. septicum* antitoxin, and 1000 units *Cl. œdematiens* antitoxin.

Films and agar cultures were prepared from the local lesion, the spleen, and the blood of each animal. Positive reactions showed inflammatory lesions at the site of the inoculation, with extensive gelatinous œdema in the subcutaneous tissues. The spleen was enlarged and soft.

*Results*

In all, 1053 samples were taken. 64 were from Argentine cattle, 532 from East African cattle, 144 from West African cattle, 250 from West African goats, and 63 from West African sheep. Hides are divided by the trade into grades—1, 2, and 3 in descending order of quality—and samples from each grade were examined separately within each of the major groups. The final collated results were:

| | *Samples taken* | *Number positive for anthrax* | *% positive for anthrax* |
|---|---|---|---|
| *Argentine cattle* | | | |
| Grades 1 and 2 mixed.. | 64 | 2 | 3·1 |
| *East African cattle* | | | |
| Grade 1 .. .. | 147 | 11 | 7·5 |
| Grade 2 .. .. | 169 | 21 | 12·4 |
| Grade 3 .. .. | 216 | 34 | 15·7 |
| *West African cattle* | | | |
| Grade 1 .. .. | 76 | 35 | 46·1 |
| Grades 2 and 3 .. | 68 | 14 | 20·5 |
| *West African goats* | | | |
| Grade 1 .. .. | 92 | 28 | 30·4 |
| Grade 2 .. .. | 75 | 28 | 37·3 |
| Grade 3 .. .. | 83 | 33 | 39·7 |
| *West African sheep* | | | |
| Grade 1 .. .. | 17 | 8 | 47·0 |
| Grade 2 .. .. | 25 | 16 | 64·0 |
| Grade 3 .. .. | 21 | 6 | 28·6 |

*Conclusions*

The anthrax organism is widespread in imported hides, and it is likely that at least one hide in four is contaminated. The cleanest hides seem to be those from Argentine cattle (3·1% contaminated), while the most dangerous are those from West African sheep (48% contaminated). Commercial grading is unrelated to the incidence of anthrax infection.

### Discussion

Two facts have to be considered. First, anthrax is exceedingly rare among the Liverpool dockers—a labour force notoriously unwilling to accept special physical restraints. Secondly, about one in four of the many hides they handle has the anthrax organism on it.

In view of the ubiquity of the organism in dry hides, the low incidence of the disease in relatively unprotected workers can only mean that under normal conditions the anthrax bacillus is unable to attack human tissue successfully. This conclusion suggests that future measures against the disease need not necessarily take the form of more physical precautions. (These might require specially appointed unloading-berths and, in addition, a disinfecting process which would considerably reduce the value of the hides.) If the occasional case of anthrax is due to a failure of resistance in a particular individual or to unusual virulence in the attacking bacteria, better results might perhaps be obtainable by raising the immunity of the workers.

In 1954, Dr. Wright and Dr. Wedum, of Frederick, Maryland,[1] developed an inoculation against anthrax for use in man which gave good immunity. Darlow et al.[2] showed that antibodies neutralising anthrax toxin can be demonstrated in the blood of those immunised: and that reactions to immunisation (including booster doses) are never severe enough to cause absence from work. In future this form of protection might well be offered to all who normally work with hides and other material known to be a source of anthrax. We are investigating the possibility of using it in the port of Liverpool.

### Summary

In a sampling survey of imported dry hides in Liverpool in 1958 a high proportion of hides were found to be contaminated. Anthrax, however, is very rare among those handling them.

To explain this anomaly, it is suggested that the natural human resistance to anthrax must be greater than is generally supposed.

For further protection against the disease, reliance should perhaps be placed on immunising procedures rather than on the extension of physical precautions.

Our thanks are due to Prof. D. T. Robinson, director of the Public Health Laboratory, Liverpool, for undertaking the bacteriological investigations of samples, and to Mr. R. H. Winter, of a hide-importing firm, for cooperation in the actual sampling.

## Domiciliary Midwifery

Dr. R. J. Donaldson, the medical officer of health, records in his annual report that at the end of 1958 there were three vacancies for midwives in Rotherham. Domiciliary-midwifery cases totalled 816 in 1958, compared with 757 in 1957; and patients discharged from maternity hospitals before the fourteenth day totalled 541, compared with 425. 19 expectant mothers who were recommended on social grounds for admission to hospital could not be accepted owing to lack of accommodation; in many instances application was made very late in the pregnancy, but nevertheless the home environment was totally unsuitable for confinement. "In operating a domiciliary midwifery service in these circumstances one soon comes to the view that a town the size of Rotherham should have a more adequate hospital midwifery service."

## Arsenic on Potato Crops

Owing to the absence of rain, potato crops sprayed with haulm destroyers containing arsenic may this year present a greater risk than usual to potato pickers. The Ministry of Agriculture, Fisheries and Food has strongly advised growers to postpone lifting the crop for as long as possible after arsenic has been sprayed. Whenever possible, potato pickers should wash their hands and faces before eating, drinking, or smoking.

The handling of potato plants within ten days after having been sprayed with arsenic is forbidden by law unless the workers wear overalls, rubber gloves, rubber boots, and dust masks.

1. Wright, G. G., Wedum, A. G. Proceedings of Symposium on Anthrax in Man held at University of Pennsylvania. Philadelphia, 1954.
2. Darlow, H. M., Belton, F. C., Henderson, D. W. *Lancet*, 1956, ii, 476.

# Conferences

## TUBERCULOSIS

FROM A CORRESPONDENT

THE 15th conference of the International Union Against Tuberculosis, held in Istanbul on Sept. 14–18, was attended by about 1200 doctors from more than 60 countries. The list of subjects discussed is impressive: chemoprophylaxis, B.C.G. vaccination, atypical mycobacteria, relapse after medical and surgical treatment, indications for surgical treatment, new antibacterial drugs, health education, the role of the public-health nurse, rehabilitation, and acquired immunity to tuberculosis.

The main impressions from attending these meetings and from talking " in the lobbies " are that there is still a vast amount of tuberculosis in the world, and that we still have much to learn about the disease. There is a wide gulf in the outlook between doctors from the more technically and socially advanced countries and those from the poor and economically under-developed ones. To the one group the more interesting questions may be rare infections with mycobacteria other than tubercle bacilli and important but relatively small differences between certain regimes of treatment: to the other group the important topics are more likely to be how tubercle bacilli themselves are to be detected and how any regime of treatment at all can be given to the millions requiring it. The first group may tend to look askance at any measures of detection and treatment that do not meet the scientific standards they would require in their own countries—though it was clear that these standards are not uniformly high. The second group may possibly feel that their own urgent problems of improvisation seem too little understood by the more fortunate.

Some indication of these trends was given in a discussion of proposals put forward by Dr. Johan Holm, of W.H.O., for trying to reduce and finally eradicate tuberculosis. That trained technicians could be trusted to read X-ray films as normal or abnormal was not generally acceptable, though no alternative was suggested to enable more tuberculosis to be detected in countries without enough doctors to do the work. The suggestion that all people with abnormal X-ray shadows thought to be tuberculous should be treated by anti-tuberculosis drugs, by " mass-production " methods without further attempts at diagnosis, was severely criticised—certainly on good grounds in some respects. But has any other feasible suggestion been put forward to deal with the millions of tuberculous patients living with hunger and poverty, too few hospitals and tuberculosis clinics, too few doctors and nurses, and no hope of cure?

That we have still much to learn about tuberculosis was well shown in the discussion on B.C.G. It is now generally accepted on incontrovertible evidence that this vaccine can produce protection against disease. There are, it appears, still a few who question this; but they have perhaps not considered the evidence critically. Recent studies of the Medical Research Council have shown that in Britain a high degree of protection of adolescents persists for at least $6^1/_2$ years. Ten years ago B.C.G. vaccination was a highly controversial subject in this country at the time when mass-vaccination campaigns were being carried out in many parts of the world. Now it is an accepted public-health measure in Britain; but at the same time doubt is growing, in at least one country where such campaigns began many years ago, whether it is locally as effective as it was expected to be. Such doubts do not by any means imply that B.C.G. vaccination should be discontinued as a mass preventive measure; they merely indicate that there is still much to be discovered about immunity in tuberculosis and that the scope for further research is immense.

In a smaller way, the discussions on new drugs and relapse brought out the deficiencies in our knowledge. Is cycloserine, for instance, as highly effective as some speakers claimed, or as little effective as others suggested? What really is the necessary duration of chemotherapy to prevent relapse in different categories of patients? Is failure of chemotherapy caused only by inefficient drug regimes and irregular drug taking, or is it unavoidable in some cases, beyond both the skill of the physician and the control of the patient?

About 40 doctors from Great Britain attended the conference, and this country was well represented in the discussions. But there are less than 20 individual British members of the International Union Against Tuberculosis, compared with approximately 250 in France. Great Britain is undoubtedly making important contributions to the elimination of tuberculosis in the world through its own research and the example of its own practice. But it might be wondered whether we support international work sufficiently. As less of our resources of money and knowledge are required to fight our own battle against tuberculosis, should we not be giving more to help others fight theirs?

## DEPRESSION

THE gathering held on Sept. 21–26 at Clare College, Cambridge, under the ægis of the Postgraduate Medical School was an occasion of considerable psychiatric significance. Introducing it, Sir AUBREY LEWIS pointed to the relative neglect of investigation into the affective disorders compared with schizophrenia. It was a popular error to regard depression as well under control with physical methods, as the work of Norris and others had shown, and it remained a major social problem. In an attempt to break away from traditional Kraepilinian nosology, European workers had developed new concepts; the " unitary psychosis " of the 19th century, for example, had been revived, particularly by Conrad, who had described typical endogenous depression as a prelude to schizophrenia. The diagnostic system of Kleist, the approach of the existentialists, and the tendency in America for diagnosis to be rejected, all reflected a common discontent, and these trends, although Sir Aubrey doubted their value, could not be ignored by psychiatrists here. Recent work linking anxiety with depression supported the view he had long held against opposition that these conditions and involutional melancholia were united in affective disorder by the common form of sadness. New light on suicide might arise from the frequent association with previous head injury noted in Germany and Finland, and in the biochemical field the retention of sodium, seen in depression, seemed to implicate the pituitary-adrenal axis. Sir Audrey concluded with the observation of Henri Ey that " . . . it is precisely

in connection with depression that all the great problems of psychiatry have originated".

### Cyclic Phenomena

In an address notable for its broad clinical wisdom, Dr. JAMES FLIND laid stress on the importance of interviewing the patients' relatives and on the diurnal cycles of symptoms, such as sweating, in addition to the well-known rhythmic changes in mood and sleep. Examining this matter more closely, Prof. W. MAYER-GROSS described a number of curious cases with regular manic-depressive swings of different lengths; 65 had been collected alternating in this way daily, 1 for over 30 years. A patient he had examined with a 7-year illness had had hypomania one day followed by a sleepless night, a day of deep depression, sound sleep, and a return to hypomania. Such cases should be sought out, for they may answer many questions: rhythmicity, although commented on by the earliest French observers, had been neglected and we had not approached in depression the classical biochemical work of Gjessing on periodic catatonia. Dr. Mayer-Gross reviewed a wide field of biological study on the mechanism of the "physiological clock". Periodic phenomena in plants and animals proved remarkably resistant to imposed changes in environment, and their survival value to the organism was often obvious. For us, however, it was less clear: perhaps human faculty was based on diurnal changes? Many mechanisms may be involved in mood control, and the action of drugs (which should be suited to the phasic changes) might only be on the target organ.

Considering the "purpose" of depression, it was suggested in discussion that suicide of unsuitable members may have survival value for society; and at the close of the conference Prof. ALEXANDER KENNEDY speculated that normal fluctuations in mood may be a protective mechanism against stress and grief. The exhaustion state after great athletic feats seemed related to depression, and he commented that the depressive does not laugh or make love: he was lying fallow. Perhaps the illness was the price we paid for being such complicated organisms. There was still a need, he said, to make wild guesses about this condition and to send more hypotheses to the experimentalists for testing; perhaps, for example, some of the 140 adrenocortical steroids were involved in the mechanism?

### Psychological Aspects

Approaching the problem from the Pavlovian standpoint, Dr. RUSSELL DAVIS defined depression, for his purpose, as a more or less general reduction of response to external stimuli. This he believed to be due to repeated stimulation without reinforcement, analogous to the experimental extinction of a conditioned reflex: thus depression was a consequence of frustration. Producing such a situation experimentally led firstly to a phase of overactivity; the subject being alert, anxious, and apprehensive. Secondly, there was some disintegration of the sensory field and selective preoccupation with one aspect of a task to the neglect of the remainder. Finally inertia appeared with a general decline and delay in responsiveness, discouragement, and dejection. Other studies showed shrinkage of the perceptual field with "funnelling" of attention: the anxious person found it harder to come to correct interpretations of dimly lit pictures and made many more erroneous guesses. Implications for treatment were that behaviour should again be rewarded and that therefore any task should be of such a level that the patient could succeed in it. He should not continue with matters beyond his reduced ability. Apparently, too, as he found the assessment of sensory data hard, he had a need for information. Some speakers wondered how far Dr. Davis' operational definition was relevant to depression as seen clinically and whether the simple ideas of excitation and inhibition could be applied to its complex phenomena. The analogy of "giving information" to psychotherapy was thought interesting, for here one was trying to give the patient knowledge of his unconscious processes.

Presenting the psychoanalytical view, Dr. W. HOFFER reviewed developments since the early observations of Abraham on sadistic conflicts and Freud on mourning and melancholia. Self-esteem, characteristically lowered in the depressive, was more easily shaken at times of physiological change, and the analyst, like Sir Aubrey Lewis, did not find it useful to distinguish between reactive, endogenous, neurotic, or psychotic depression. On the other hand, Dr. Hoffer saw very clear differences between depression and anxiety (though they could coexist), the former being a state of hopelessness and the latter of helplessness. As to therapy, he surprised some of his audience by his belief that even severe depressions could be treated by analysis under the correct circumstances. The love/hate/guilt situation was open to ventilation, though memory might have to be reconstructed from verbal and non-verbal clues and from transference behaviour—but even silence could be therapeutic. The task became harder with improvement, as suspicion and anger were acted out and suicide might occur: group therapy made this more difficult to control. Dr. Hoffer described some points of technique and said that psychotherapy could very well accompany or follow physical methods. That self-knowledge made recurrence less likely was, Dr. Hoffer admitted, unproven, but he hoped people would not be too unjustly critical because controlled techniques were denied to the psychoanalyst.

Prof. O. L. ZANGWILL mentioned the work of his predecessor MacCurdy, who, as a heterodox Freudian, saw behaviour as a response to instinct which was variably obstructed and which gave rise to depression if the situation got out of control, though Professor Zangwill thought clear instincts hard to accept in humans. The use of posthypnotic amnesia showed that unconscious material could cause an affective response, and he believed the criticisms of psychotherapy were on unsure ground because of faulty methodology; techniques were needed, and he thought that so far it was as if one were using a photometer to measure the beauty of a picture. He was not one of those, however, who believed that there was "nothing organic about organisms" and advocated a neurological approach to the subject.

### Neuropharmacology and Therapeutics

One thing which made the time particularly appropriate for such a symposium was the emergence for the first time of drugs acting on the depressive mood. Surveying the various drugs and some of their actions, Dr. ERIK JACOBSEN (Copenhagen) pointed out that all the important discoveries had arisen from the chance observations of psychiatrists.

Prof. JACKSON A. SMITH (Chicago) subjected a large mass of published work on drugs to a review that was bitingly critical and highly entertaining. A constantly recurring theme was the need for uniform and meaningful classification, and Professor Smith recalled one paper recently where subdivisions of depression ran to no less than nineteen. Fallacious or biased methodology came in for particular criticism and results were often conflicting. The average success-rate for drugs in research where controlled methods had been used ran out at 25%, but uncontrolled studies on the same drugs showed average success of 83%. Follow-up of treated cases was often neglected, and it was salutary to ask an alcoholic after you had treated him how many previous cures he had overcome. Asking a colleague if he followed the subsequent progress of his patients, he was told, "Once, but never again." Professor Smith seemed doubtful about the value of most of the amine-oxidase inhibitors and said the enthusiasm of the therapist was usually more effective than the action of the drug. These powerful agents should not be pressed indefinitely, and if there were no response after a reasonable interval the drug should be stopped. When assessing side-effects one needed to recall that placebos, too, produced "toxic" symptoms in some people.

Dr. LEMPERIERE and Dr. PIERRE DENIKER (Paris) agreed with other workers that iproniazid was most valuable in endogenous

depression and also that treatment should be long-continued and withdrawn cautiously. With imipramine, hippocampal spikes on the E.E.G. might herald convulsive phenomena, but the drug was quite different in properties from the amphetamines and from chlorpromazine. Study and follow-up of 137 cases showed an overall complete-remission rate of 22%, which, when added to the "marked improvement" group, rose to 60%. Restricted to the "frankly melancholic" this figure became 74%. Dosage was 150–200 mg. per day by injection for 12 days, replacement by oral therapy and gradual withdrawal after recovery. Over 300 mg. could be given, but this was a toxic dose, and poor physical health indicated caution. Results were best with cyclic psychoses (the least suggestible) and poorest with neurotic and psychopathic cases. Replacing with placebo led to return of symptoms.

Prof. C. L. CAZULLO (Milan) reported basically similar results in 171 patients given imipramine. He gave up to 350 mg. per day, and of chronic endogenous cases 49% gave a "positive" and 24% a "fair" result. Failures often did well when E.C.T. was added. 10% of his cases experienced brief hypomania responding to sedatives.

The absence of an English contribution on drugs was noted by Continental colleagues but, as Prof. ERWIN STENGEL commented, the insistence on scientific control made psychiatrists slow to publish their findings. Such demands for control were criticised by some, and the virtues of the pilot study in which one gets the "feel" of a drug were extolled: ideally both are required, the planning of the second depending on the impressions from the first, as Professor KENNEDY pointed out.

### Physical Methods

Presenting clinical impressions derived from his unique experience, Prof. LUCIO BINI (Rome) believed that E.C.T. modified by relaxants gave results that were just as good as unmodified E.C.T.; but the shock should never be combined with promazine or reserpine. Endogenous cases did best, and the mode of action was unknown, although neither the asphyxia nor the convulsion was essential, and successful treatment during sleep had ruled out psychological factors: he considered that the effect was on the brainstem. It was noteworthy that he thought E.C.T. was often given excessively and in the wrong cases, listing minor depression, circular cases with a short cycle and, oddly, involutional cases showing anxiety and paraphrenic features as particularly unsuitable. Imipramine, he believed, was indicated for mild cases.

Dr. WILLIAM SARGANT agreed that E.C.T. was often abused, and he advocated starting with 1 or 2 in the first week and giving a weekly shock with strict reappraisal between, until remission occurred. Involutional cases and those waking early did best, he thought, and normal sleep or hysterical or anxiety symptoms militated against a good result, especially palpitations on the couch prior to treatment. Timing was important, for cyclic cases often had a "refractory period" in which E.C.T. did not work, followed by a phase of remission in which the illness could be quickly ended. Imipramine had impressed him less than iproniazid and was more expensive. Regarding leucotomy, Dr. Sargant emphasised the importance of an adequate cut through the lower medial quadrants of the frontal lobe, and results had been good in over 80% of his cases. It was worth reoperating in some failed cases and careful clinical judgment was always required; he rejected 3 out of 4 patients offered for the operation. A good underlying personality, a 2-year illness, and a greater period sick than well were among his criteria. Physical treatment was being overshadowed by the startling possibilities of drug control, and Dr. Sargant looked ahead to the time when depression would again be treated by the ordinary doctor.

Dr. E. BERESFORD DAVIES, who was largely responsible for the successful arrangement of the meeting, gave the closing address, a wise clinical discourse.

The proceedings of this admirably organised symposium, including the 16 group discussions and closing summaries, are to be published in full by the Cambridge University Press.

## In England Now

*A Running Commentary by Peripatetic Correspondents*

WHEN we were children the tinkers belonged to our Highland scene. Mysterious in their migrations, they seemed different and formidable somehow. Perhaps it was their aloof independence. Or their importunity on your doorstep or in your kitchen. But how tactfully they merged into the landscape! What sensitivity made them choose dim black or sherry-brown for their arched tents? The blue of their smoke was the brightest hue about their encampments. Even the tartan shawls of their women blended graciously with moss and heather. Their only leavings were a few ashes.

Now those tinkers have vanished, and a different race of migrants camp by the burns and on the green levels. They do not invade your house with tinpails and bunches of pot-scrubbers. But how their angular turquoise or emerald tents assault you. And their caravans seem over-emphatic in hospital white or pale yellow. Even half a dozen plastic buckets assert themselves on a machair. Not to mention the drifts of litter.

But I am no artist. And someone else may quote the public-health regulations. I was thinking about attitudes.

* * *

It occurred to me one night as a not very enthralling play drew to a close that the customary performance of God Save the Queen in theatres and cinemas was a necessary and important preserver of health. When one has been seated in heat for three hours one loses one's peripheral circulatory tone; if one starts to walk suddenly a severe, although temporary, fall in blood-pressure may take place, possibly with syncope and certainly with momentary cerebral hypoxia. By standing still for a few minutes these bad effects can be minimised. Those who run out of the cinema to escape the National Anthem do not realise that injured health is the alternative to this brief discipline.

Since a too prolonged standstill is as deleterious as a too abrupt resumption of the erect posture (cf. Guardsmen), it follows that there is an optimum length of National Anthem. One verse of God Save the Queen must approach this. Chinese, Dutch, and Ethiopian custom seems to exceed it. Nigeria now seeks a new National Anthem: one can only hope that it will be chosen on physiological principles.

* * *

*Overheard outside registry office.*—"The young person who gets married today resembles the average listener—if he can get reasonably pleasant reproduction he isn't really interested in high fidelity."

* * *

The holiday ordeal is nearly over. I seem to have spent most of the days trying to start an outboard motor which has stopped, and most of the nights trying to stop a baby which has started crying (when not trying to stop it starting).

Much of the remaining time has been spent disentangling fishing lines, thus gaining practice for disentangling kite strings. Both activities are a waste of time anyway, for there is as little chance of a kite flying for me as there is of a fish being foolish enough to take any bait that I may offer. The hooks break off one by one as I catch rocks or seaweed; occasionally the line and sinker goes as well. My conspicuous lack of success as a fisherman does not dismay me, for a far bigger worry would be what to do with any fish I caught. I carry a penknife to cut the line in this eventuality—for even if I don't catch a conger eel, I would be no more enthusiastic about unhooking any other threshing denizen of the deep.

I do enjoy painting, but the wind has been strong and I have sacrificed artistic integrity to the extent of painting from the car the best compromise of my subject allowed by parking facilities. It is obvious that I needed a holiday as my language when a canvas was caught by a playful gust of wind was surprising, and the scandalised uxorial correction only served to enhance the kudos I gained among the children. Never mind, I shall be able to work it off on the weeds when we get home.

* * *

In my student days we called it the Fundamental Physiological Fallacy, because it was more evident in the teaching of physiology than in other subjects; not that the anatomists were guiltless, mind you. I mean the fallacy whereby the predilections of the teacher outweighed the needs of the student, so that instead of teaching us how the body worked, they taught us how they found out how it worked. It was enough to produce a lifelong prejudice against what may be called the kymographic approach. What did we care which end of the frog Morgagni tied up with string? We wanted to know whether his results still held water. In anatomy, too, we felt that on "where" took too much precedence over the more interesting questions of "how" and "why."

One cure I have heard suggested was for us to be taught anatomy by the physiologists and physiology by the anatomists, and looking back on it all now, I am inclined to think there may be something in that solution, though I would prefer, on reflection, to be taught physiology by a pathologist. And pathology? By a physician, surely? And medicine? By a psychiatrist. And psychiatry? By a general practitioner, of course. And general practice? By an expert in time and motion study. And time and motion? That's where the anatomist would get his own back.

* * *

Your would-be publican correspondent might have found the answer to his problem of nomenclatures if he had driven along one of the more harrowing stretches of the A30. What better choice for an obstetrician's hostelry than the *Baredown Inn*?

* * *

Marking borrowed books is a crime for which no penalty is too drastic; but I admit that I enjoy making notes in my own books. Usually I confine my efforts to a line in the margin, or an expostulatory ?, or perhaps !! It gives me a pleasant feeling of superiority, and there is no danger that the author will answer back.

When I was younger I was more verbose. On rereading the mutilated volumes I realise that most of my annotations were peculiarly useless. Why, for instance, did I find it necessary to write "absolute rot !!!" beside a mild statement with which I now entirely agree? And what could I have meant by "? mackintosh"?

I'm looking forward to an enjoyable evening with my latest book. It has wide margins and well-spaced type. The only snag is that it is second-hand, and some obtuse bibliophobe has already put lines by the sides of utterly unimportant paragraphs. I shall have to rub them all out before I can settle down to study it properly.

* * *

VIVA

O what is the answer you seek
Sir
What is the answer you seek?
I am perfectly docile and meek
Sir
But it seems that my wits are too weak.

I haven't the slightest idea
Sir
No I haven't the slightest idea;
You may think I have been at the beer
Sir
But I feel it is probably fear.

I've really got nothing to say
Sir
I've really got nothing to say;
Kindly hurry me quickly away
Sir
And examine me some other day.

I have no information to tell
Sir
I have no information to tell—
Let us pray for the sound of the bell
Sir
To deliver us both from this hell.

# Letters to the Editor

## NEOLOGOPOIESIS

SIR,—Your leading article of Sept. 12 begins:

"The basis of sickle-cell disease is the presence of an abnormal hæmoglobin molecule which in its reduced state forms aggregates. A multimolecular combination of this hæmoglobin, being much less soluble than single molecules, becomes a solid gel; this is birefringent and its constituents form a single tactoid."

I guessed that "birefringent" means "doubly refractive," a term which I learnt in my youth, but "tactoid" beat me. Fearing that my ignorance was due to senility (and recollecting Gulliver's discovery that "The Language of the Country being always upon the Flux, the *Strulbrugs* of one age do not understand those of another") I asked a young friend who is reading for her finals. She could not help me. I hope her examiners are equally ignorant. Of all the books I consulted the only one that mentioned the word was *Blakiston's New Gould Dictionary*. I appreciate that as *The Lancet* covers the whole field of medicine many of its articles are written for the benefit of specialists and are therefore fully intelligible only to them. But I suggest, with the greatest respect, that a leading article should be intelligible to all your readers. Here it needed only a few words of explanation to make all the difference to the reader between understanding and enlightenment on the one hand and irritation and discouragement on the other.

In your issue of Aug. 15, an article by Dr. B. G. Edelston is headed Thesaurosis following Inhalation of Hair Spray. Nowhere in the article does the writer mention "thesaurosis", let alone any connection between that word and "hair spray". He refers to your annotation [1] entitled Thesaurosis, in which the opening sentence says in so many words that one more substance is added to those that accumulate in the reticulo-endothelial system. To find the connection one would have to search the articles mentioned in the annotation. "Thesaurosis" is not mentioned in the British medical dictionaries I have consulted. *Dorland's Dictionary* defines it as a condition "resulting from the storing up in the body of unusual amounts of normal or foreign substance". It therefore seems to be a grandiloquent term for "cumulative poisoning". *Blakiston* gives the same definition but goes one better, calling the condition "thesaurismosis". Θησαυρός we know from *Roget's Thesaurus*, but there must be many who do not know the original meaning—storehouse.

This throws an interesting light on the technique of neologopoiesis (a word I have invented to keep my end up). Someone coins a word and it gains a very limited currency. In your annotation you accept it, on very inadequate grounds, as an established word that needs no definition. Subsequent writers, seeing it in so prominent a place as a *Lancet* annotation, assume that it is on everyone's lips. So "thesaurosis" (or "thesaurismosis", if you prefer) comes to stay though few know what it means. The use of esoteric words with no explanation of their meaning encourages that most dreadful thing—a cult confined to the few who have been initiated into its mysteries.

In the science of neologopoiesis the Americans are far ahead of us although they are much less steeped in the classical tradition than we are. One of them has written a large book which shows how to find a pseudoclassical word for every conceivable (and barely conceivable) condition. Intercourse between husband and wife should be called "virgynation"; with a prostitute, "cypripareunia"; between three persons (a triumph of copulative skill, one would imagine), "troilism". Lust especially felt in the morning is "matutolagnia", and a male's enjoyment of being teased, "tantalolagnia".

To find the meaning of most of the neologisms now appearing at the rate of, it is said, 1000 a year we have to consult the

1. *Lancet*, 1958, i, 1058.

ponderous American dictionaries, for no British publisher has the financial resources to embark on a venture of equivalent magnitude. Greatly as we admire the Americans for their medical achievements we cannot but view with misgiving our tacit acceptance of the take-over bid for medical nomenclature that their superior resources enable them to make.

Although I agree with your refusal [2] to ban neologisms, I suggest, again with the greatest respect, that it would be helpful to your readers if you did not assume on their part a knowledge of the meaning of words that few of them can be expected to possess and that can be found (and even then not invariably) only in the large and not readily accessible American dictionaries.

Chesham, Bucks. FFRANGCON ROBERTS.

*** Dr. Ffrangcon Roberts is not alone in his difficulty: another reader writes to condemn our opening paragraph on Sickle Cells as "a masterpiece of medical jargon." Their irritation springs from a problem of communication which is becoming increasingly grave, and the last thing we want to do is to aggravate it. When we discuss, however, a subject, such as sickling, whose expanding terminology is unfamiliar to a great many people, we find it harder and harder to avoid terms that may give pain to those who cannot at once tell a tactoid [3] from a tomato. Nevertheless, we maintain that the offending paragraph is a clear summary of a difficult subject, readily understandable to those who know the language, and that Dr. Ffrangcon Roberts is asking too much, even of editors, when he urges us to translate these new languages into more familiar terms. We hope we can do something to keep those who speak different languages in touch with each other, but we believe it would be unreasonable to resist implacably the esoteric terminology that Dr. Ffrangcon Roberts deplores.—ED. L.

## THE ST. THOMAS'S OPERATION FOR ULCERATED LEGS

SIR,—It is six years since Cockett and Elgan Jones [4] brought to our notice the work of Robert Linton of Boston, who in 1938 [5] described an operation for ligation of the communicating veins of the lower limb in post-thrombotic legs. Since that time I have seen 11 patients who have had this operation (6 of them were operated on at St. Thomas's Hospital and the remainder by other general surgeons). 3 complain solely of pain and tightness in the lower leg. 8 have ulceration in the long operation scar. All have œdema.

When I was in the U.S.A. in 1956 I found that Linton and his associates were almost the only people who still believed in this operation. Others had tried it and abandoned it as causing more harm than good.

The St. Thomas's paper [4] was written in 1953 when the authors had operated on a considerable number of patients, but no long-term follow-up of these cases has appeared. Yet this is an operation (like the ill-fated Bauer operation [6] for post-thrombotic legs) which is seized upon avidly by general surgeons to whom these ulcerated legs are tedious and exhausting, and who are only too happy to find some new surgical technique with which they hope to relieve their clinics of vast numbers of chronic patients. Even in a recent report [7] from St. Thomas's the operation is merely reiterated with no details of results.

The crux of the matter is this: are patients with post-thrombotic legs better after this operation than before? I believe some are, but equally I believe they would have been just as fit if the operation had not been carried out. For in addition to the operation they had treatment in a large and efficient physiotherapy department which schools them in *bandaging*—the bandage which so many of them have to continue to wear for months, or for ever, after the operation. It is the bandaging which improves their legs.

Physical methods alone can achieve much; and the effects of an operation can be misleading when it is supported by a physiotherapy department. Unlike varicose ulcers, post-thrombotic ulcers cannot be *cured* until such time as we can put new valves into veins, but they can be healed. It takes on average thirteen weeks [8] with ambulatory methods, and after this the large majority will keep well, having been taught the principles of venous return and bandaging.

A post-thrombotic ulcer cannot be diagnosed from an "ankle-flare" any more than tuberculosis can be diagnosed from an increased pulse-rate. Yet, so far as I can judge from what has been written [7] by those who favour this operation, this "ankle-flare", or even the mere presence of an ulcer, is often sufficient reason for attaching the "post-thrombotic" label. In point of fact not more than 15% are post-thrombotic. The great majority (70%) are varicose,[8] and whereas post-thrombotic ulcers cannot be cured, only healed, varicose ulcers can be both cured and healed—healed by elastic adhesive ambulatory compression and cured by operation on the superficial veins. But when a *varicose* ulcer is treated by the St. Thomas's operation, in which not only are the superficial veins dealt with but, in the mistaken conviction that it is a post-thrombotic ulcer, the ankle blow-outs are dealt with too, the patient is only healed, *not* cured. For she is often left with a tender indurated lower leg which may require permanent bandaging, instead of a normal leg free for ever from ulcers and varicose veins.

The London Varicose Clinic, S.W.11. STANLEY RIVLIN.

## THE ÆTIOLOGY OF LEUKÆMIAS

SIR,—The article by Dr. Schöyer (Sept. 19) illustrates the type of thinking which seriously inhibits much cancer research today. It indeed contributes more than anything else to any "deadlock" (to use his own word) which may exist.

In the first place he tacitly assumes (as does Osgood whom he quotes) that increased rate of cell division is synonymous with autonomous growth. An increased rate of division in the abnormal cells of a cancer is a prerequisite for the display of the other characters of those cells; but those other characters, which give the cancer its invasiveness, its capacity to metastasise, and its capacity to interfere with the function of other bodily systems, must also be accounted for by any useful hypothesis of the ætiology of malignancy. This may seem a tall order, and indeed at the moment it is, but the solution of the problem is not made any easier by concealing difficulties, or pretending that they do not exist.

Secondly, his hypothesis of the change in the sensitivity of some nuclear genes conforms with most general hypotheses of malignancy in only restating what we already know—namely, that the cancer cell is different from the normal cell and that it passes these different characters on to its descendants. If Dr. Schöyer would like to suggest by what biochemical and biological routes his hypo-

2. *ibid.* 1958, ii, 215.
3. Tactosols are colloidal solutions containing non-spherical particles ("tactoids") which are capable of orienting themselves.
4. Cockett, F. B., Elgan Jones, D. E. *Lancet*, 1953, i, 17.
5. Linton, R. R. *Ann. Surg.* 1938, **107**, 582.
6. Bauer, G. *Brit. med. J.* 1950, ii, 318.
7. Cockett, F. B. *Practitioner*, 1959, **183**, 19.
8. Rivlin, S. *Lancet*, 1958, i, 1363.

thetical nuclear lesions may influence those cellular and tissue mechanisms which normally maintain a regular numerical, spatial, contactual, and functional relationship between the cells of an organ or tissue, all of us interested in the behaviour of the cancer cell will indeed be grateful.

Department of Experimental Pathology, and Cancer Research, School of Medicine, Leeds. JOHN O. LAWS.

## AIDS TO ARTIFICIAL SPEECH

SIR,—In your issue of July 11, there were descriptions of appliances for the production of artificial voice (p. 38) and an annotation on this subject (p. 31). I have recently used the apparatus described by Mr. R. V. Tait (who kindly made it available to me) to help a patient with ascending paralysis who required treatment with positive-pressure respiration. As often happens in these cases, the patient was unable to move upper or lower limbs, but fortunately maintained good movement of the bulbar and facial muscles. Since he could not write, he found communication very difficult after tracheostomy had been performed, but was able to make himself understood quite well after only 24 hours' practice with the oral vibrator. He has now recovered to the extent that his tracheostomy can be closed, and he speaks very highly of the contribution which this device made to his peace of mind during the period when he was on positive-pressure respiration.

Edinburgh J. B. STANTON.

## DEATH AFTER FIRST TREATMENT WITH ELECTROPLEXY, THIOPENTONE, AND SUXETHONIUM BROMIDE

SIR,—The cause of death in the case of prolonged apnœa due to suxethonium bromide, described by Dr. Campbell (Sept. 19), seems to be circulatory failure due to asphyxia (anoxia and carbon-dioxide accumulation) due to the prolonged effect of a depolarising-type muscle relaxant. Many cases of prolonged apnœa due to suxamethonium chloride (succinylcholine) have been described by Harper,[1] Hewer,[2] Love,[3] and Evans.[4] Although the hydrolysis rate of suxethonium bromide is 50% faster than suxamethonium chloride, its action on the muscle end-plate is the same—i.e., preliminary stimulation followed by more prolonged depolarisation.

When prolonged apnœa is present at the end of a surgical operation many factors have to be taken into account in reaching a diagnosis:

(1) *Respiratory centre depression* by narcotics, barbiturates, and anæsthetic gases.

(2) *An alteration in carbon-dioxide tension*, either an increase leading to carbon-dioxide " narcosis " and respiratory depression, or a decrease resulting in acapnia.

(3) *Factors which tend to maintain high concentrations of relaxant at the endplate*—e.g., dehydration, oligæmic shock, hypotension, hypothermia, overdosage, poor renal function, or low pseudocholinesterase level.

(4) *Factors which tend to potentiate the effect of the relaxant at the endplate*—e.g., electrolyte imbalance (especially low potassium concentration) (Keating [5]) or the presence of other anæsthetic agents, such as ether.

(5) *Special features of the relaxant*—e.g., the occurrence of dual blockade, mixed blockade, or high concentration of succinylmonocholine.

1. Harper, J. *Brit. med. J.* 1952, i, 666.
2. Hewer, C. L. *ibid.* p. 971.
3. Love, S. *Anæsthesia*, 1952, **7**, 113.
4. Evans, F., Gray, P. W. S., Lehmann, H., Silk, E. *Lancet*, 1952, i, 1229.
5. Keating, V., Tang, K. *Anesth. Analg.* 1957, **36**, 32.

The case described is relatively uncomplicated by these additional factors and the diagnosis seems to me to rest between (1) dual blockade, or (2) a low pseudocholinesterase level.

The use of atropine followed by 5–10 mg. of edrophonium (' Tensilon ') will give a quick response if the cause of the prolonged apnœa is dual blockade. This can then be followed by atropine and up to 2·5 mg. of neostigmine. This was done successfully in 2 personal cases, one in which the apnœa after a single dose of 40 mg. of suxamethonium chloride had lasted two hours. If it is due to a low pseudocholinesterase level, infusion of fresh frozen plasma will restart respiration.[6]

The management of a case of prolonged apnœa under the conditions described is passage of an endotracheal tube and inflation with nitrous oxide (to maintain hypnosis) and oxygen, with carbon-dioxide absorption. While artificial ventilation is being carried out there is no deterioration in the patient's condition and no urgency. A careful review of the drugs given will indicate the most fruitful line of treatment.

St. George's Hospital, London, S.W.1. D. M. DAVIES.

## POTASSIUM-SECRETING TUMOURS OF THE LARGE INTESTINE

SIR,—The following case should prove the existence of potassium-secreting tumours of the large intestine and give the data required by Dr. Abbott and his colleagues in their letter of Sept. 5.

Our patient had a colostomy performed 9 months ago for subacute intestinal obstruction due to a tumour of the rectum. The colostomy has worked perfectly, producing one well-formed motion per day, but he is losing about 8 oz. of a thin, clear, mucous fluid per rectum every day. His serum-potassium is 3·75 mEq. per litre and the mucous fluid contains 137·5 mEq. of potassium per litre. He has been on a normal diet and has not shown any signs of hypokalæmia, except some general myasthenia, but since the appearance of this correspondence in your columns, he has been put on potassium supplements.

Central Pathological Laboratory, Burnley, Lancs. G. BEHR.

## BEDS FOR CONFINEMENT

SIR,—In what purported to be a factual survey of the Emergency Bed Service, Dr. Abercrombie (Sept. 19) wrote that " nothing is done until the patient goes into labour " when the conditions of her home make it unsuitable for a confinement. This statement has been seized upon by the popular Press to justify a serious misrepresentation of the local health authorities in the London area. Of this area the County of Middlesex forms a not inconsiderable part, and some facts about the working of its antenatal services may help to put the problem in its setting.

In 1958 the total number of births in the county was 27,282. During the six months ending in March, 1959, there were 73 E.B.S. cases, making an average of about 146 a year, or 1 in 187. If the 9317 hospital confinements are taken separately the E.B.S. cases are 1 in 64.

When a patient's home conditions are unsatisfactory every effort is made to arrange for the confinement to be in hospital, but two difficulties arise. (*a*) Patients with poor home conditions very often do not bother to make their pregnancy known until it is well advanced and hospital beds that might have been available have already been booked. (*b*) Some obstetricians book at an early date such a high percentage of the beds in the units they control that no beds are available when application is made later by the local health authority for the accommodation of cases of social need. Time and again the doctor in a local health authority clinic will spend half the morning on the telephone attempting to find a bed for a patient who cannot have her baby at home. It is simply not true to suggest that

6. Levin, J. Personal communication, 1958.

the local health authority takes no action until the patient is in labour and then telephones the E.B.S. Calls are made on the E.B.S. only because all earlier applications for a hospital bed have been turned down.

As for the babies born in ambulances: of the 73 cases mentioned above as admitted to hospital through the E.B.S. not a single birth has taken place in an ambulance.

Your annotation makes proposals that would go a long way towards solving the problem if conditions were created to make them possible. With the staffing of maternity units and the domiciliary service in its present state, a more rapid turnover of hospital patients would not only increase the already heavy pressure of work in the hospitals but would cause a breakdown in the domiciliary service. There will have to be some costly improvements in the salaries and conditions of work of midwives if the number needed is to be obtained. There would then be an opportunity for some promising experiments with small units in which the mother was delivered by the domiciliary midwife with her general practitioner in charge, and returned home under their care after two or three days.

A. P. WHITFIELD
Principal Medical Officer,
Maternity and Child Welfare,
Middlesex County Council.

County Health Department,
London, S.W.1.

## SELECTION AT CELLULAR LEVEL AND THE ECOLOGY OF TUMOURS

SIR,—It seems that when Mr. Frost wrote his letter of Sept. 12 he had not read what I have written concerning the cause of cancer, otherwise he would not write of "the enormous improbabilities associated with randomness being disposed of". The mathematics of a random distribution about a mean is fairly well developed and I have shown how this might account for the evolution of cancer cells. The random distribution of plasmagenes describes the appearance of what Ephrussi [1] has called "vegetative littles" in yeast populations and the observations of Mather and Jinks [2] on the genetics of *Aspergillus glaucus*.

Mr. Frost need no longer be in doubt that this subject has ever been approached from his point of view before. The ecological approach to the problem of somatic cell populations is an old one. It is worth calling attention to two discussions in the literature, Ephrussi's Withering lectures,[1] and Burnet's *The Clonal Theory of Acquired Immunity*.[3]

London, S.E.3. G. E. LOXTON.

## ADMINISTRATION OF DRUGS IN HOSPITALS

SIR,—I was not at all surprised to see a letter from Mr. Trillwood in your issue of Sept. 12 following my paper the previous week. I was, however, disturbed to note that Mr. Trillwood continues to insist that doctors should learn to write prescriptions so clearly and perfectly that even trainee nurses can interpret them with certainty and without any danger to the patient. I would point out that the Minister of Transport has a similar task in his plea for careful driving.

If Mr. Trillwood would again study my paper he would find the answer to all his questions, including the very important point that the original prescription shall be checked against the file entry each time the drug is given. I can assure Mr. Trillwood that, like himself, I have sat on committees to discuss this very difficult problem and that the scheme discussed in my paper was the result of many years' work and experience.

The enthusiastic reception of the scheme by medical and nursing staff, particularly the staff nurses responsible for drug administration, and the absence of serious criticism following its introduction, has led me to believe that the scheme is indeed a good one.

Gerrards Cross,
Bucks. P. J. FOWLER.

1. Ephrussi, B. Nucleo-Cytoplasmic Relations in Micro-organisms: their bearing on cell heredity and differentiation. Oxford, 1953.
2. Mather, K., Jinks, J. L. *Nature, Lond.* 1958, **182**, 1188.
3. Burnet, M. The Clonal Selection Theory of Acquired Immunity.

## ÆTIOLOGY OF PICA

SIR,—I noted with interest your annotation (Sept. 5) concerning the ætiology of pica. An association between iron-deficiency anæmia, malnutrition, and pica was suggested, and supported by its occurrence in Brazil and parts of Africa. This was contrasted with the paucity of such cases in this country. The following case, recently observed in the neighbourhood of Salisbury Plain, may be of interest.

A little girl aged two years had had a history of pica since the age of eighteen months. At that age she began to ingest garden soil, and later resisted all efforts to correct this. For the ten days before she was first seen, all other solids were refused. Examination revealed a thin pale child of normal length for her age. The weight was 23 lb.—i.e., equivalent to the 50th percentile for a child of fifteen months. There was no other clinical abnormality.

The hæmoglobin was 65% (colour index 0·9). After admission to hospital, her appetite returned forthwith, and before any treatment of her anæmia was attempted.

This case seems to be in contrast to those described by Lanzkowsky [1] and also to the conclusions drawn in your annotation.

Tidworth Military Hospital,
Hants. D. BARLTROP.

## PENICILLIN IN LEPTOSPIROSIS

SIR,—Prof. L. P. Garrod,[2] reviewing a book on leptospirosis in which reference is made to the work of Fairburn and Semple,[3] writes:

"Conclusions on therapy are pessimistic: the value of immune serum is not adequately proved and there is no good evidence of benefit from penicillin or other antibiotics *given at a time when a diagnosis is usually made*. No attempt is made to reconcile this finding with the high susceptibility of the organism in vitro—*a discrepancy for which there must be some explanation*" (my italics).

Provided the penicillin that Fairburn and Semple used was not of reduced potency, the explanation must be that the date of onset of the illness (and also the date that penicillin therapy was instituted) was underestimated—a common failing among relative newcomers to the tropics and subtropics in the ten years' extensive experience of febrile illness of one of us in many parts of Egypt, The Sudan, Eritrea, Syria, Palestine, Japan, and Malaya. The stoical Gurkhas are prone to be most casual about the onset of symptoms and unless persistently questioned are apt to underestimate the duration of their illness. In this they are closely matched by their brothers-in-arms from the United Kingdom.

There is no doubt that when penicillin is given early enough, often enough, and in large enough doses to United Kingdom and Gurkha soldiers in Malaya there occurs a reaction which is diagnostic of leptospirosis and which was designated the diagnostic penicillin leptospiral response.[4] Within twenty-four hours or so such patients felt and looked as new men. The change was

1. Lanzkowsky, P. *Arch. Dis. Childh.* 1959, **34**, 140.
2. Garrod, L. P. *Brit. med. J.* 1959, i, 907.
3. Fairburn, A. C., Semple, S. J. G. *Lancet*, 1956, i, 13.
4. Mackay-Dick, J., Robinson, J. F. *J. R. Army med. Cps.* 1957, **103**, 186.

spectacular. Medical officers who have witnessed this reaction have expressed astonishment that attention had not been drawn to it before.

In the 21 penicillin-treated cases of Fairburn and Semple [3] this reaction must have passed unnoticed or it never occurred at all. If the latter, that is confirmatory evidence in our opinion that penicillin therapy was instituted later than they thought. At this point it should be stressed that such was the severity of this penicillin leptospiral reaction in some of our cases early on in our series [4] we almost decided to abandon the use of penicillin entirely as treatment in leptospirosis until the significance of this reaction from a diagnostic and therapeutic point of view suddenly became apparent.

Semple [5] suggests that our phantom controls [6] probably exhibited a different distribution of serological types. We cannot accept that as a relevant criticism and wonder on what grounds he makes such a suggestion. In any case were the controls of the penicillin-treated cases in the work of Fairburn and Semple balanced serotype for serotype? [3 5]

In our experience, which is supported by others,[7] adequate penicillin given early enough and often enough in human leptospirosis is not only specific treatment but the reaction which accompanies its administration is characteristic and diagnostic.[4 6 7] Also, as we have stated before, no matter how late the presumptive diagnosis of leptospirosis is made penicillin should be given.[4]

Connaught Hospital (Army Chest Centre), Hindhead, Surrey. JOHN MACKAY-DICK.
The London Hospital, Whitechapel, E.1. JOHN F. ROBINSON.

## BIOCHEMICAL EFFECT OF PHENYLACETIC ACID

SIR,—My colleagues and I are grateful to Dr. Milne (Sept. 26) for pointing out an alternative explanation for some of our findings (Sept. 12). In view of the doubtful clinical response to phenylacetic acid in our patients despite an apparent biochemical improvement, his hypothesis concerning the decreased 5-hydroxyindoleacetic-acid excretion we observed is obviously worth testing on suitable subjects.

Whichever interpretation is the correct one, however, our main purpose was to draw attention to a new approach to the symptomatic treatment of the carcinoid syndrome. Even though phenylacetic acid has proved therapeutically ineffective, we feel that other inhibitors of 5-hydroxytryptophan decarboxylase, such as the chalcones [8] or α-methyl-DOPA,[9] must be given a trial should animal experiment prove them sufficiently non-toxic.

Few experimental studies have been carried out on in-vivo inhibitors of 5-hydroxytryptophan decarboxylase as such. Recent work [8 10] would appear to indicate however that this enzyme is identical with DOPA decarboxylase. It is probably valid therefore to project some of the conclusions from the more extensively studied DOPA decarboxylase inhibition to the consideration of 5-hydroxytryptophan decarboxylase inhibition. Clark [11] has surveyed a large number of DOPA decarboxylase inhibitors and, although it is difficult to draw a comparison between his in-vitro and in-vivo findings, it is obvious that a number of the compounds he investigated show a more effective inhibition in vivo than in vitro. This being the case, Dr. Milne's inference, calculated from in-vitro data of Davison and Sandler,[12] that the oral dosage of phenylacetic acid given to our patients would be insufficient for 5-hydroxytryptophan decarboxylase inhibition, simply does not follow. We certainly agree that an appreciable proportion of administered phenylacetic acid is metabolised to phenylacetylglutamine, but would point out that this conjugation takes a finite time, during which period some free acid would be in circulation. Whether it proves to be a true in-vivo inhibitor of 5-hydroxytryptophan decarboxylase must be decided in the future. But if it does possess this action, we might expect renal concentrations of the enzyme, with their preferentially high blood-flow, to be especially vulnerable.

There is good evidence to suggest that when 5-hydroxytryptamine appears in the urine in high concentration, as in the atypical carcinoid syndrome,[13] its presence is due to direct renal decarboxylation of 5-hydroxytryptophan. Whilst small quantities only of 5-hydroxytryptamine are excreted after its parenteral administration,[14] intravenous,[15–17] or intraperitoneal [18] 5-hydroxytryptophan results in the appearance of large amounts of 5-hydroxytryptamine in the urine, as does direct renal perfusion of 5-hydroxytryptophan.[19] Certainly, but a fraction of the amounts of 5-hydroxytryptamine involved would cause a disturbance of renal hæmodynamics if introduced into the afferent circulation.[20] Likewise, there is a direct renal conversion of DOPA to dopamine [11 21] and it is of interest that this reaction has been used as a test of DOPA decarboxylase inhibition.[11] Animal experiments have disclosed a decreased urinary excretion of 5-hydroxytryptamine together with an attenuation of toxic signs if large doses of 5-hydroxytryptophan are preceded by phenylacetic-acid administration.[18] Viewed in this light, it is difficult to escape the conclusion that there may have been at least some degree of renal 5-hydroxytryptophan decarboxylase inhibition in our patient who responded to phenylacetic acid by a decreased 5-hydroxytryptamine output.

London, W.6. M. SANDLER.

## SUPPLIES OF CARCINOID TUMOUR TISSUE

SIR,—I should be very grateful to obtain large amounts of carcinoid tumour tissue from patients with the full "flushing" syndrome. The tissue should be as fresh as possible and arrangements would be made to collect it.

Medical Unit, St. Mary's Hospital, London, W.2. W. S. PEART.

## INCURABLY OF UNSOUND MIND REDEFINED

SIR,—Your report of Aug. 22 (p. 180) directs attention to a problem which is of concern to psychiatrists as well as to the legal profession. In this connection it is appropriate to refer to a recent publication [22] entitled Errors in Prognosis in which I. L. Hitchman reviews the status of a series of patients from whom spouses were granted divorces on the basis of the patients' being "permanently and incurably insane with no hope of recovery". These patients subsequently improved to the point that the author admits a definite error in prognosis to have been made at the time of the judicial proceedings.

Hitchman states that she now has added a phrase to her testimony in divorce cases, saying that "at the present state of our medical knowledge", the patient has to be considered permanently and incurably ill. Moreover, she has made it a rule not to testify in divorce cases unless the patient had had adequate and prolonged treatment with ataractic drugs without improvement.

Seaside Memorial Hospital of Long Beach, California. GEORGE X. TRIMBLE Director of Medical Education.

5. Semple, S. J. G. *Lancet*, Sept. 5, 1959, p. 289.
6. Mackay-Dick, J., Robinson, J. F. *ibid.* 1959, i, 100.
7. Cook, A. T. *ibid.* Aug. 1, 1959, p. 81.
8. Yuwiler, A., Geller, E., Eiduson, S. *Arch. Biochem. Biophys.* 1959, **80**, 162.
9. Westermann, E., Balzer, H., Knell, J. *Arch. exp. Path. Pharmak.* 1958, **234**, 194.
10. Fellman, J. H. *Enzymologia*, 1959, **20**, 366.
11. Clark, W. G. *Pharmacol. Rev.* 1959, **11**, 330.
12. Davison, A. N., Sandler, M. *Nature, Lond.* 1958, **181**, 186.
13. Sandler, M., Snow, P. J. D. *Lancet*, 1958, i, 137.
14. Erspamer, V. *R.C. sci. Farmitalia*, 1954, **1**, 1.
15. Davidson, J., Sjoerdsma, A., Loomis, L. N., Udenfriend, S. *J. clin. Invest.* 1957, **36**, 1594.
16. Brengelmann, J. C., Pare, C. M. B., Sandler, M. *J. ment. Sci.* 1958, **104**, 1237.
17. Pare, C. M. B., Sandler, M., Stacey, R. S. *Lancet*, 1958, ii, 1099.
18. Davison, A. N., Ruthven, C. R. J., Sandler, M. 1959 (to be published).
19. Sandler, M., West, G. B. 1959 (to be published).
20. Hollander, W., Michelson, A. L., Wilkins, R. W. *Circulation*, 1957, **16**, 246.
21. Holtz, P., Credner, K., Koepp, W. *Arch. exp. Path. Pharmak.* 1942, **200**, 356.
22. *Sth. med. J. Bgham, Ala.* 1959, **52**, 591.

# Medicine and the Law

## The Podola Trial

THE Podola trial raised a number of important medicolegal issues which may be the subject of considerable debate. For the moment, however, comment must be restricted by the possibility of an appeal.

Guenther Fritz Podola, a 40-year-old Canadian of German birth, was charged with the capital murder of Detective-Sergeant Purdy by shooting; he was at the time being held on another charge. At the outset of the trial, the defence submitted that Podola was unfit to plead in that he was suffering from hysterical amnesia and had lost all memory of the events surrounding his arrest and the alleged shooting. Counsel for the Crown contested this plea. The amnesia was not genuine; and, even if it were genuine, it did not follow that the accused was unfit to plead.

Subject to any directions on law by the judge, the question whether an accused person is fit to plead is always one of fact to be decided by the jury after hearing evidence.[1] Whether Podola was suffering from amnesia, as claimed, was a question of fact for the jury; if the jury had found that the claim was genuine, it would have been for the judge to decide as a matter of law whether this could found a plea of unfitness, and to direct the jury accordingly.

Before evidence was called, Mr. Justice Edmund Davies had to decide where the onus of proof lay. After legal argument, he held that it was for the defence to show, on a balance of probabilities, that the accused was suffering from amnesia. (This was, however, a lighter burden of proof than that which rests upon the Crown in prosecuting a criminal charge.) His Lordship thus declined to follow the ruling of Mr. Justice Salmon in an earlier case that, where a prisoner's fitness to plead was in issue, the onus of proof lay upon the Crown.[2]

The evidence, which lasted several days, was only partly medical. In addition to the doctors who were called by both sides, both Podola and his solicitor gave evidence; there were also other witnesses on questions of fact.

In his summing-up,[3] Mr. Justice Edmund Davies said it was in the public interest that such a charge as capital murder should be disposed of as speedily as it could be properly and fairly, but no man could be brought for trial unless he was physically and mentally capable of standing trial. That was a cardinal principle of law which went back hundreds of years and was recognised by Act of Parliament in 1800 when it was decided that, if a man was found insane and could not be tried, then the jury's verdict was to that effect and certain steps were taken in relation to it.

His Lordship told the jury that they were not concerned with how the word "insane" in that statute should be interpreted, but the defence submission gave rise to an issue of fact which they had to decide. "This is not a trial by doctors. They are here to give their opinions."

Referring to the claim that a man was unfit to plead if he was suffering from amnesia, the judge said that there was no recorded case in this country of such a submission being made before. There had been such a claim in one case in Scotland. His Lordship went on to say: "Such a plea is, of course, easy to advance, and it may be extremely difficult to refute and to challenge. It provides an obvious and convenient refuge to a person finding himself or herself in a position of grave difficulty and danger. And, of course, the greater the danger, the greater the motive for making an assertion of this kind. But unique though such a submission is in my experience and easy though it is to put forward such an assertion, your duty is to examine it with scrupulous care and determination to do justice."

Reviewing the evidence, Mr. Justice Edmund Davies said that the defence doctors had said that Podola had manifested the well-known symptoms of hysterical amnesia which seemed unhappily to have been given a French description—*la belle indifférence*. This was, his Lordship said, one of the crucial matters, and thereafter he would call it indifference. His Lordship concluded by asking whether the whole of the evidence, medical and non-medical, satisfied the jury that the probability was that Podola was suffering from hysterical amnesia, loss of memory, which was claimed. "If, on the balance, you think the answer is 'yes', and the defence have proved it, then you will say so. If, on the other hand, your view is that the burden of proof on the defence has not been discharged, you will answer the question in the negative."

While the jury were considering their verdict, the judge heard legal argument.

Counsel for the Crown submitted that, even if the jury returned a verdict that the amnesia was genuine, that was not a ground on which the defence could found a plea of unfitness to plead. There appeared to be no case in England in which it had even been argued, let alone decided, that where a defendant was otherwise sane and normal, amnesia relating to the time of the commission of the offence made him unfit to plead. Perhaps that was not altogether surprising when one examined what would be the result if such a proposition were to become the law. "In every case where a man, through drunkenness let us say, was unable to remember what happened, or where a motorist suffered concussion with consequent loss of memory following an accident in which he might be charged with an offence, that person would be unfit to plead."

In reply, counsel for the defence said that it was a little dangerous to consider this question against a background of some other defendant with some other degree of amnesia on some other charge. Without a memory Podola could not make a defence. "The very essence of the matter is that he should have such comprehension so as to enable him to make a proper defence. Indeed, one's mind boggles at the position of a man who cannot make a defence because of some disturbance of the mind."

In the event, the judge gave no ruling on this point because the jury concluded that Podola was not suffering from a genuine loss of memory. The major point of interest from a medicolegal standpoint therefore remains unresolved.

On the judge's direction the jury then found that Podola was sane and fit to stand trial. At the trial which followed, Podola was found guilty of the charge of capital murder and sentenced to death.

## The Litigant Patient

The Minister of Health has issued a memorandum offering hospital authorities guidance about the release of information about patients who are taking, or contemplating, legal action against the hospital or a third party.[1]

Where a request for records or reports is made on manifestly insubstantial grounds, the hospital cannot be

1. *Lancet*, 1959, i, 1200.
2. R. *v.* Sharp, 1957, 41 Criminal Appeal Reports 197.
3. *Manchester Guardian*, Sept. 22, 23, 1959.

1. H.M. (59) 88.

expected to grant it; but where information is being sought in pursuance of a claim of substance against the hospital or a member of its staff, the decision is more difficult. Each request, the Minister suggests, must be examined on its own merits, in the light of legal advice, and in consultation with any member of the medical or dental staff concerned in the claim. Though the production of case-notes and similar documents is not obligatory before the stage of discovery in the proceedings is reached, the Minister feels that boards and committees, as they are public authorities, would neither wish nor be well advised to maintain their strict rights except for some good reason.

Where the information is required in litigation between the patient and a third party, hospital authorities should be prepared to help by providing, as far as possible, the information, subject always to the consent of the patient. Sometimes the information sought may be entirely unrelated to medical matters—e.g., the date of the patient's admission or discharge, or whether he was a private patient and signed the appropriate form of undertaking. Such information may properly be given by the secretary of the board or committee without reference to the medical staff. But in all medical matters—e.g., where information is wanted about the diagnosis, details of treatment, or prognosis—the doctor who was in charge of the patient's treatment at the hospital, or his successor, should be consulted, even when the request is only for extracts from the case-notes. Reports about accidents prepared in accordance with H.M.(55)66 are privileged documents.[2]

Where the request for information does not come from the patient, but from some other party who is engaged in legal proceedings with him, no information of any kind should be supplied without the patient's written consent, unless the witness or document has been subjected to subpœna or discovery by the Courts. The only other exception to this rule should be where information is sought on behalf of another hospital board or committee (or a member of their staff), against whom the patient is bringing proceedings.

2. See *Lancet*, Aug. 1, 1959, p. 83.

# Obituary

## WILLIAM SANTON GILMOUR

O.B.E., M.B. Lpool

Dr. W. Santon Gilmour, medical superintendent of the Killingbeck and Gateforth Sanatoria, Leeds, died at Colby, in the Isle of Man, on Aug. 31, at the age of 61.

After qualifying from the University of Liverpool in 1921, he held appointments in tuberculosis at the David Lewis Northern Hospital, Liverpool, at the Ministry of Pensions Hospitals, Sunderland, and under the Welsh National Memorial Association. In 1931 he was appointed medical superintendent of Killingbeck Sanatorium. During the late war, when his sanatorium was taken over for use as a fever hospital, he was in charge of the civil defence organisation in Leeds. When he found that Leeds was not being bombed, he volunteered to serve in London during the worst of the blitz. He was appointed O.B.E. for his work in 1942.

In 1943 he was asked by the Colonial Office to study the incidence of tuberculosis in the West Indies, and he later undertook similar investigations in China and in Uganda for the United Nations. In 1951 he was appointed chairman of the technical advisory panel on chest diseases of the Leeds Regional Hospital Board.

Of his work at Leeds G. F. E. writes:

"Santon Gilmour guided the affairs of chest diseases in the Leeds region through the last eight years of progressive change and reorientation, and he leaves behind him well-formulated plans for the future. His gift for organisation and administration was most effective in committee where his diplomacy and tact, and his talent for persuasion and conversion to new ideas, were often successful.

"His publications were not prolific, but everything he had to say, whether by the spoken or written word, was always apposite, significant and valuable. He was a clinician of the old school, who considered that help and guidance for the patient as a whole was more important than the simple management of the disease process. It was this ability constantly to consider all his patients as individuals and to approach all their problems as purely personal ones which endeared him to them. To those who did not know him well he seemed shy and somewhat reserved, but to his intimates his conversation and company were always scintillating and amusing, and often provocative, and his death on sick leave in Colby, where he was born, while making arrangements for his retirement, came as a great blow to his friends."

G. H. T. also pays tribute to his relationship with his patients:

"Dr. Santon Gilmour was always approachable, courteous, and sincere. He would go to endless trouble to help, encourage, and advise those who sought to draw from his wide experience. He understood the trials and the tribulations of others, and he showed great skill in handling people. We shall remember the many hours he gave to the welfare of his patients and the hospitality of his home, where it was his wont to discuss the problems of the day."

Dr. Santon Gilmour leaves a widow and a son.

## RIPLEY ODDIE

B.A., B.M. Oxon.

Dr. Ripley Oddie, for many years medical director of Bayer Products, Ltd., died at his home in Chelsea on Sept. 20 at the age of 57.

The son of Mr. S. Ingleby Oddie, a London coroner, he was educated at Rugby, Oriel College, Oxford, and St. Thomas's Hospital, where he qualified in 1927. He held a number of resident appointments at St. Thomas's and then joined the staff of a national newspaper as medical editor. In 1931 he was appointed an assistant editor of the *British Medical Journal*, and in 1935 he became medical adviser to Bayer Products Ltd. Among his duties was the editing of the company's house journal, *Clinical Excerpts*, which benefited from his experience of journalism. In 1939 he was made a director of the firm. Early in the late war he volunteered for the R.A.F., and was a wing-commander when he was invalided out.

Dr. Oddie was a good all-round sportsman. He was a member of the M.C.C. and a keen golfer and skier, and his wife, formerly Miss Jeanette Kessler, was captain of the British Ladies Ski Team in 1936. When ill health prevented him from engaging in sport he took up ornithology and became an authority on British birds.

K. B. writes:

"His colleagues in Bayer Products Ltd. and his many friends will mourn Ripley Oddie as a particularly kindly man with his own very special brand of humour, for his high sense of responsibility to the company and to the medical profession, and above all with admiration for his fortitude and philosophical acceptance of the bad health which dogged him over the last few years."

A memorial service will be held at St. Bartholomew's the Great, Smithfield, London, on Oct. 14, at noon.

## BARBARA McPHERSON

M.A., M.B. Cantab.

Dr. Barbara McPherson, who died on Sept. 17 at the age of 40, was a former Prophit scholar of the Royal College of Physicians of London, where she had made a study of tuberculosis in twins and their families.

After graduating from Cambridge in 1943 she held appointments as medical registrar at Liverpool Royal Infirmary and as assistant chest physician at Islington before she was awarded, as Dr. Simonds, a Prophit scholarship in 1951. Since 1957 she was in general practice near her home at Hoddesdon. She was the wife of Dr. Angus McPherson and she leaves two sons.

P. H. writes:

"To medical research Barbara McPherson brought vitality and clarity of thinking, but she was modest and self-effacing. Tuberculosis was her main research interest, and she took part in a Medical Research Council field study of the specificity of the tuberculin reaction. As Prophit scholar she undertook, with the cooperation of many chest physicians, a large-scale epidemiological investigation on tuberculosis in twins. She described some of this important work to the first International Congress on Human Genetics, Copenhagen, in 1956, and to the Eugenics Society in 1957. She had intended to complete this report and then to make a study of family patterns in sarcoidosis, but the onset of her illness led her in 1957 to withdraw from specialist activities, and, with characteristic fortitude, to throw her great energies into full-time general practice. She continued until shortly before her death."

# Diary of the Week

OCT. 4 TO 10

**Tuesday, 6th**

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
5.30 P.M. Prof. C. N. Woolsey (Wisconsin): Organisation of Somatic Sensory and Motor Areas of the Cerebral Cortex.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary, Leeds.) Sir Francis Walshe: What We Have to Unlearn About the Anatomy and Physiology of the Nervous System.

**Wednesday, 7th**

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. R. G. Robinson; Hydatid Disease Affecting the Nervous System. (Hunterian lecture.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *History of Medicine.* Mr. W. J. Bishop: Historical Cases of Autosurgery.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. R. W. Riddell: Tinea and Moniliasis.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. F. Lee Lander: Asthma.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) Dr. C. E. Sykes: Modern Anæsthesia. (Presidential address.)

**Thursday, 8th**

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. L. E. C. Norbury: Gordon-Watson and St. Mark's Hospital. (Gordon-Watson lecture.)

ROYAL SOCIETY OF MEDICINE
5 P.M. *Ophthalmology.* Mr. B. W. Rycroft: Observations on Corneo-Plastic Surgery. (Presidential address.)

LONDON HOSPITAL MEDICAL COLLEGE, Turner Street, E.1
4.30 P.M. Sir Russell Brain: Neurological Tradition at the London Hospital. (Schorstein lecture.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Mr. A. T. Gray: Ointment Bases.

INSTITUTE OF NEUROLOGY
5.30 P.M. Prof. J. Z. Young: The Nature of Living Memory Stores.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 P.M. (Rembrandt Hotel, Thurloe Place, S.W.7.) Dr. Eric Hudson: Every Physician, Almost, Hath His Favourite Disease.

**Friday, 9th**

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, S.E.5
4.30 P.M. Sir Clement Price Thomas: Carcinoma of the Lung. (Thomas Percy Legg lecture.)

INSTITUTE OF NEUROLOGY
4.45 P.M. Dr. J. A. V. Bates: The Electrode and the Neurosurgeon.

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. With the Royal Medico-Chirurgical Society of Glasgow. (Adam House, Chambers Street, Edinburgh.) Dr. H. R. Maclennan, Mr. E. L. Farquharson (for), Dr. J. S. Robson, Prof. Ian Donald (against): That Preoccupation with the Science, as Opposed to the Art, of Medicine Has Led Us to Neglect Many of its Humanities.

# Notes and News

## PLANS FOR HOSPITAL BUILDING

THE Minister of Health has announced how much money he hopes to spend, subject to Parliamentary approval, on hospital building and modernisation during 1960–62,[1] and how he proposes to allocate it.

At the end of 1958 he announced [2] that it was proposed to spend £25½ million on capital development in hospitals in England and Wales during 1960–61, and no change is proposed in the allocations which the hospital boards have already been informed that they may expect to receive from this provision.

During 1961–62 it is expected that altogether £31 million will be available for hospital building. The Minister proposes to continue and expand his programme of centrally financed large projects, and plans to use £15 million for this purpose. Allocations to regional boards for their own projects will be increased by a total of £500,000. The Minister has also decided to continue with his programme of plant replacement, and is to provide £3 million in 1960–61 for distribution to the boards for this purpose. The boards are asked to submit for consideration forecasts for work of this kind which they hope to undertake in 1961–62.

In 1961–62 £1½ million is to be set aside to enable boards to modernise mental and mental-deficiency hospitals. This money is intended to be spent on work which will be additional to the boards' ordinary capital programme, and in allocating it the Minister will give preference to the regions where the need is greatest.

## NEW HOSPITAL IN HERTFORDSHIRE

ON Sept. 22 Mr. Derek Walker-Smith, the Minister of Health, laid the foundation stone of a general hospital which will serve Welwyn Garden City and the new town of Hatfield. The hospital, which lies midway between these two centres, ii to cost over a £1½ million, and it is hoped that the main part will be finished in 1962.

Wards for general medical, surgical, and obstetrical cases occupy the upper floors in the wings of the T-shaped building. All have a sun lounge and balcony, and each of the ten wards has 30 beds (6 single rooms and 6 four-bed cubicles). The patients' rooms are arranged in suites of 15 beds with baths, lavatories, and showers. Nursing care is carried out from a base in the middle of the ward. On each floor there are bedrooms for relatives who need to stay over-night and accommodation for consultants for private interviews. A 24-bed ward for children is on the ground floor which will have access to a terrace and the gardens. Psychiatric patients will be treated in an annexe, which will have 100 beds as well as accommodation for day-patients.

The main clinical and servicing departments are in the stem of the building near the wards and main lift systems. Thus the pharmacy and records departments are at lower ground floor, conveniently central for the whole hospital. The casualty department with its separate entrance is at ground floor so that patients can be easily transferred to any part of the hospital. It has its own theatre and X-ray suite and is alongside the fracture clinic. A full range of pathological services has been planned and will include a central sterile department. There will be four X-ray suites for diagnostic radiology and four fully equipped theatres with a pressurised ventilating system. The maternity department occupies one complete floor of the building and has 60 beds. The outpatient department has a separate entrance near the hospital approach and occupies two floors of an extended wing at the tail of the main building. It will be comfortably furnished and will have a snack bar and a special room for children.

## TUBERCULOSIS IN AFRICA

OPENING the ninth session of the World Health Organisation Regional Committee for Africa at Nairobi on Sept. 17, Dr. F. J. C. Cambournac, director of the African Region, said that nearly every country in the region had now asked for the services of the two W.H.O. tuberculosis survey teams. A third team was being formed. A centre for the analysis and coordination of tuberculosis work in Africa was shortly to be set up in

1. H.M.(59)86.
2. See *Lancet*, 1958, ii, 1376.

Nairobi, where epidemiological information would be gathered for control campaigns. Several mass chemoprophylaxis projects were already under way in territories of the region, including Kenya and Mauritius.

### University of London

On Oct. 12, 14, and 15, at 5.30 P.M., at University College, Gower Street, W.C.1, Prof. C. D. O'Malley (University of California Medical School), will speak on Andreas Vesalius.

### University of St. Andrews

Dr. J. S. S. Stewart has been appointed lecturer in surgery in Queen's College, Dundee.

### Royal College of Surgeons of England

On Thursday, Oct. 29, at 5 P.M., at the college, Lincoln's Inn Fields, London, W.C.2, Mr. H. R. Thompson will give a Thomas Vicary lecture. He will speak on Sergeant Surgeons to Their Majesties.

### The Thyroid Gland

The Royal Faculty of Physicians and Surgeons will hold a conference on this subject from Nov. 11 to 13 at the Faculty, 242, St. Vincent Street, Glasgow, C.2. Particulars will be found in our advertisement columns.

### Royal Institute of Public Health and Hygiene

Dr. Denis Hill will give the Bengué lecture on Monday, Oct. 12, at 4 P.M., at the institute, 28, Portland Place, London, W.1. He will speak on the role of psychiatry in medicine.

### Association of Anæsthetists of Great Britain and Ireland

The annual meeting of this Association will be held on Oct. 22 and 23 at Stratford upon Avon. Details may be had from the hon. secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2.

### Course on Epilepsy

The University of Liverpool is holding lectures on this subject on Wednesdays at 8 P.M. from Oct. 14 to Dec. 2. Dr. Robert Coope will give the first lecture, and other speakers will include Dr. R. R. Hughes, Mr. R. H. Hannah, Dr. Ivan Leveson, Dr. Anne McCandless, and Dr. R. G. R. Burrows. Tickets (6*s*.) may be had from the director of extramural studies, 9, Abercromby Square, Liverpool, 7.

### World Clean Air Conference

The National Society for Clean Air is holding a conference in London from Oct. 20 to 23 to celebrate its diamond jubilee. Representatives from 29 countries will attend. Further information can be had from the offices of the society, Palace Chambers, Bridge Street, S.W.1.

### Presentation to Dr. W. N. Goldsmith

A dinner in honour of Dr. W. N. Goldsmith, who is retiring as director of the department of dermatology of University College Hospital, London, was held on Sept. 24, when his past and present dermatological colleagues at U.C.H. presented him with a silver inkstand.

### American College of Chest Physicians

Entries are invited from medical students all over the world for this college's 1960 prizes for essays on "any phase of the diagnosis and treatment of chest diseases (cardiovascular and pulmonary)". In 1959 the first prize ($500) was awarded to M. A. Salmon of the Middlesex Hospital, London, for a review of pulmonary hydatidosis. Further particulars may be had from the college, 122, East Chestnut Street, Chicago 11, Illinois, U.S.A.

### Biochemical Journal

Dr. A. G. Ogston has resigned from the chairmanship of the editorial board of this journal. The committee of the Biochemical Society have appointed Dr. W. V. Thorpe as his successor. Correspondence and communications should still be sent to the secretary to the editorial board, Lister Institute of Preventive Medicine, Chelsea Bridge Road, London, S.W.1.

### Research Cooperation between U.S.A. and Russia

The U.S.A. and Russia are to cooperate in research on cancer, heart-disease, and poliomyelitis. This was announced after talks between American and Soviet health officials at the National Institutes of Health, Bethesda, Maryland (*Times*, Sept. 28). Before the talks opened, Dr. Aleksandr M. Markov, who is a member of the Collegium of Public Health and chief of the Kremlin medical service, said: "Between our two countries there has been a certain lack of contact. The contacts we have had have certainly been fruitful. We should like to extend them" (*New York Times*, Sept. 26).

### Ophthalmological Society of the United Kingdom

The annual congress of this society will be held at 1, Wimpole Street, London, W.1, from March 31 to April 2, 1960. The programme includes a discussion on the visually defective infant and a symposium on hormonal exophthalmos. Particulars may be had from Mr. L. G. Fison at the offices of the society, 47, Lincoln's Inn Fields, W.C.2.

---

Prof. A. L. Banks has left for India, where he is to spend a year at Lucknow University as visiting professor of social and preventive medicine for the World Health Organisation.

The Coventry and District Voluntary Blood Donors' Association is to make an annual award of £25 for an "outstanding contribution to the knowledge of blood transfusion or the science of hæmatology". The award is open to any person of any age, or nationality, for work done in Great Britain. Applications, or nominations, for this year's award should be sent to the hon. general secretary of the Association, Mr. L. G. Griesbach, 6, Delhi Avenue, Coventry, Warwickshire, not later than Dec. 31.

Semipermanent exhibitions will be held during the winter at the Institute of Dermatology, Lisle Street, W.C.2. The first, from Oct. 5 to 26, will be by Dr. Henry Haber on histology of normal skin.

The St. Thomas's Hospital Old Students' Dinner will take place at the Savoy Hotel, London, W.C.2, on Thursday, Oct. 29, at 7.30 P.M. Tickets (£2 5*s*.) may be had from the hon. secretaries at the hospital.

The annual dinner of past and present students of University College Hospital Medical School will be held at the Savoy Hotel, London, W.C.2, on Friday, Oct. 30, at 8 P.M. Tickets (£1 16*s*.) may be had from the hon. secretary of the Old Students' Association, at the hospital.

The annual dinner of the Sheffield Medical School Old Students' Association will be held in the Firth Hall of the University, Western Bank, Sheffield, 10, on Saturday, Nov. 7 at 7 P.M. Details may be had from the secretary, department of pathology, the University, Sheffield, 10.

---

CORRIGENDUM: *Clubbing of the Fingers*.—In this leading article (Sept. 19) the statement at the foot of column 2 on p. 390 that "urinary œstrogen excretion was raised in 3 patients with arthropathy, though only 1 of these had gynæcomastia" should have been ascribed to J. Ginsburg, *Quart. J. Med.* 1958, **27**, 335 (footnote 30).

## Appointments

CLEOBURY, J. F., M.B. Lond., D.C.H.: senior assistant psychiatrist, Carlton Hayes Hospital, Narborough, near Leicester.
GRAHAM, A. J., L.R.C.P.E.: assistant port M.O., Liverpool.
HAMILTON, WINEFRIDE M., M.R.C.S., D.P.H.: assistant divisional M.O., Lancashire County Council (Prestwich area).
HOLTI, GUNTER, M.D. Leeds: physician, department of dermatology, Royal Victoria Infirmary, Newcastle upon Tyne.
MARKHAM, WINIFRED M., B.SC. Birm., M.R.C.S., D.C.H., D.P.H.: deputy M.O.H. and deputy principal school M.O., Darlington.
MAVOR, G. E., CH.M. Aberd., F.R.C.S.: consultant general surgeon, Aberdeen general and special hospitals.
MORGAN, T. N., M.D. Aberd., F.R.C.P.: consultant physician, Aberdeen teaching hospitals.
MORRIS, JOYCE M., M.B. Manc.: assistant divisional M.O., Lancashire County Council (Radcliffe area).
PRICE, E. R., M.B. Lond., F.R.C.S., M.R.C.P.: part-time consultant orthopædic surgeon, Barnsley group of hospitals.
SETTLE, H. L., M.D., M.SC. Manc., D.P.H.: M.O.H., Fulham.
STREET, D. F., M.B. Lond., D.M.R.D.: consultant radiologist, Mid Glamorgan H.M.C. group.
SUTCLIFFE, ISABELLA M., M.B. Glasg., D.P.H.: assistant school M.O., York.
VALE, R. J., M.B. Lond., M.R.C.P., F.F.A. R.C.S., D.A.: consultant anæsthetist, Guy's Hospital, London.